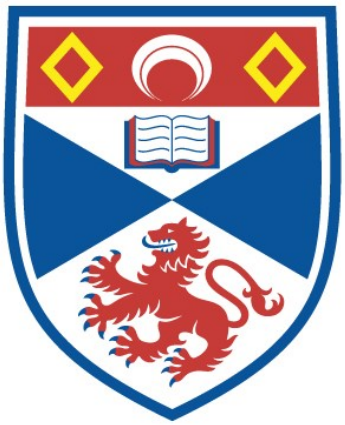
THE REACTIONS OF TERVALENT PHOSPHORUS REAGENTS WITH AROMATIC NITRO-COMPOUNDS

David John Sears

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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THE REACTIONS OF TERVALENT PHOSPHORUS REAGENTS WITH AROMATIC NITRO-COMPOUNDS

A Thesis

presented for the degree of

Doctor of Philosophy

in the Faculty of Science of the

University of St. Andrews

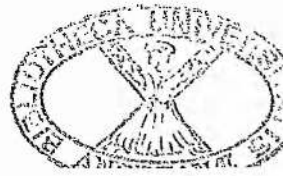
by

DAVID JOHN SEARS, B.Sc.

September, 1968

St. Salvator's College

St. Andrews.



I declare that this thesis is of my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Chemistry Department, St. Salvator's College, University of St. Andrews under the supervision of Professor J.I.G. Cadogan since 1st October, 1965, the date of my admission as a research student.

I hereby certify that David John Sears has spent twelve terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews) and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Director of Research.

ACKNOWLEDGEMENTS

I should like to thank Professor J.I.G. Cadogan for suggesting this topic of research, and for his constant advice and encouragement during the course of the work.

I should also like to express my gratitude to Dr. D.M. Smith for many helpful discussions and for the interest he has taken in this work.

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CONTENTS

INTRODUCTION

1. The Recent Development in the Organic Chemistry of Phosphorus.

The considerable expansion of organophosphorus chemistry over the last twenty years, stimulated by the many industrial applications,[1] biological uses,[2,3] and the possibility of novel routes for synthesis,[4] has led to a corresponding increase in the volume of relevant literature. Whereas the first major publication in this field, by G.M. Kosolapoff[5] in 1950, dealt solely with preparative data, more recent works[6-9] have been concerned increasingly with the details of the mechanisms of the reactions involved. A series of collected reviews[10] now supplements those found elsewhere in the chemical journals.[11-17]

This thesis describes an investigation of the reactions of tervalent phosphorus reagents with aromatic nitroso- and nitro-compounds, undertaken to extend the scope of these reactions and to clarify the mechanism. The reactions with aromatic nitroso-compounds, mentioned briefly in a review in 1962,[16] have, together with the corresponding reactions of aromatic nitro-compounds, become a subject worthy of a full review[17] over the intervening period of six years.

The versatility of tervalent phosphorus reagents in deoxygenation and reduction reactions will be outlined in a brief, and hence necessarily selective, summary. Their reactions with aromatic nitroso- and nitro-compounds will then be discussed in greater detail.

2. Deoxygenation and Reduction Reactions of Tervalent Phosphorus Reagents.

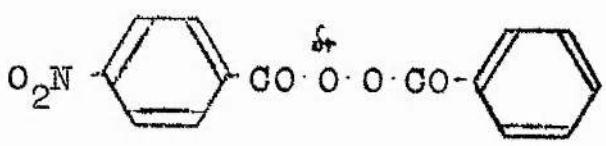
Tervalent organophosphorus compounds (X_3P), such as trialkyl- or triarylphosphines and trialkyl phosphites, react with a wide variety of oxygen-containing compounds to yield the corresponding quinquevalent derivatives (X_3PO). The major driving force behind these reactions is the great strength of the P=O bond formed, typical values for P=O bond dissociation energies in phosphates and phosphine oxides[18] lying in the range of 120-150 kcal./mole, which can be compared with values in the range 50-70 kcal./mole for the N^+-O^- bond in amine oxides.[19]

The reactions of tervalent phosphorus reagents with oxygen, sulphur and the halogens, and with compounds containing these elements, have been reviewed up to 1962.[16]

The direct oxidation by air or oxygen to the

corresponding phosphate or phosphine oxide has not yet been studied exhaustively[16] although a light-induced free-radical mechanism for these reactions has been proposed.[20,2] Triarylphosphines,[22] triaryl phosphites,[23] and trialkyl phosphites[23] all react with ozone giving excellent yields of the corresponding P=O compound, via a 1:1 adduct in the case of triphenylphosphine,[23,24] when the reaction is carried out at -70°. This adduct has recently been used as a convenient source of singlet oxygen, giving products identical to those obtained from photochemical oxidations.[24]

The reaction between diaroyl peroxides and triarylphosphines has been investigated[25-28] and found to produce the appropriate anhydride and phosphine oxide. Since no attack on the solvent occurs in these reactions, the possibility of a homolytic mechanism has been dismissed.[25] Denney and Greenbaum[29] have further shown by the use of oxygen-18 tracers that the phosphine displaces the more electropositive peroxidic oxygen in unsymmetrical peroxides (1):



(1)

In contrast, the reaction between trialkyl phosphites and dialkyl peroxides appears to be a homolytic process, Walling and Rabinowitz[30] having isolated triethyl phosphate and bi-α-cumyl from the reaction between triethyl phosphite and di-α-cumyl peroxide. They postulated a mechanism involving an intermediate phosphoranyl radical:

$$ROOR \longrightarrow 2\ RO\cdot$$

$$RO\cdot + (EtO)_3P \longrightarrow (EtO)_3\dot{P}OR \longrightarrow R\cdot + (EtO)_3PO$$

$$R\cdot + R\cdot \longrightarrow R - R$$

(where R = $PhCMe_2$)

Tervalent phosphorus reagents also reduce peresters,[31] hydroperoxides,[32] and ozonides[33] to esters, alcohols, and carbonyl compounds respectively. In each case, heterolytic reaction mechanisms involving nucleophilic attack on oxygen have been proposed.

The affinity of tervalent phosphorus reagents for both free and bound sulphur is, however, even greater than the corresponding affinity for oxygen. Thus sulphur adds readily to phosphines and phosphites in the presence of air to give the corresponding sulphide[34] (2), rather than the oxide:

$$PX_3 + S \longrightarrow SPX_3 \qquad (2)$$

The reactions may proceed via free-radical pathways, as in the reaction between triethyl phosphite and pentane-1-thiol[35] (3), in which a chain reaction involving RS· and R· radicals has been proposed [30] (4) and (5):

$$(EtO)_3P + R'SH \longrightarrow R'H + (EtO)_3P \qquad (3)$$

$$R'S\cdot + (EtO)_3P \longrightarrow (EtO)_3\dot{P}SR' \longrightarrow (EtO)_3PS + R'\cdot \qquad (4)$$

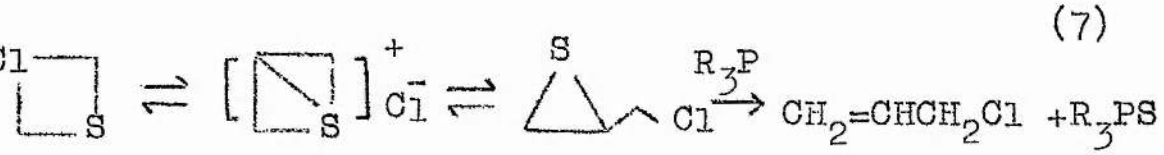
$$R'\cdot + R'SH \longrightarrow R'H + R'S\cdot \qquad (5)$$

or may be largely ionic, as in the desulphurisation of disulphides to sulphides by tertiary phosphines[36] (6):

$$Ph_3P + R\,S\cdot S\cdot R \longrightarrow Ph_3\overset{+}{P}SR \quad R\bar{S} \longrightarrow Ph_3PS + RSR \qquad (6)$$

The corresponding reaction with triethyl phosphite is thought to proceed by a homolytic pathway, in certain cases.[37]

Recently, triarylphosphines have been used to effect the desulphurisation of a number of cyclic sulphides,[38] possibly, in this example, via an intermediate thiiran (7):



(7)

and, in protein chemistry, to reduce cystinyl residues to cysteinyl residues in wool keratin.[39]

The reactions of tervalent phosphorus reagents with halogens and halogenated compounds, the last of the

three main groups of reactions discussed in the above-mentioned review,[16] have received some attention in the last few years. This has centred around the photo-initiated and thermal reactions of triethyl phosphite with carbon tetrachloride[40] and other polyhaloalkanes, and the duality of mechanism demonstrated therein. Thus the reaction may be largely heterolytic (8) or homolytic (9,10), no distinction being possible at this time between the alternative free radical processes.

$$(EtO)_3P + CCl_4 \longrightarrow \left[(EtO)_3\overset{+}{P}CCl_3\ \bar{Cl}\right] \rightleftharpoons \left[(EtO)_3\overset{+}{P}Cl\ \bar{C}Cl_3\right]$$

$$\downarrow$$

$$(EtO)_2PO\cdot CCl_3 + EtCl \qquad (8)$$

$$(EtO)_3P + \cdot CCl_3 \longrightarrow (EtO)_3\dot{P}CCl_3 \xrightarrow{CCl_4} (EtO)_3\overset{+}{P}CCl_3\bar{Cl} + \cdot CCl_3$$

$$\downarrow$$

$$(EtO)_2PO\cdot CCl_3 + EtCl \qquad (9)$$

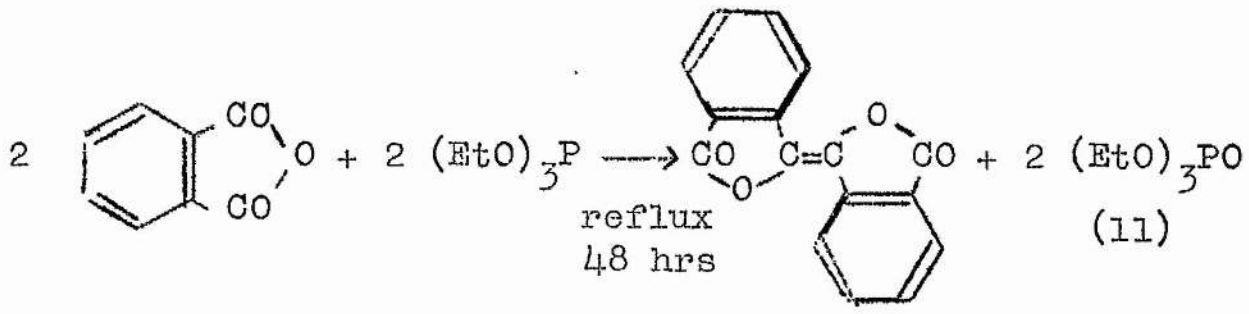
$$(EtO)_3\dot{P}CCl_3 \longrightarrow Et\cdot + (EtO)_2POCCl_3 \qquad (10)$$

$$Et\cdot + CCl_4 \longrightarrow EtCl + \cdot CCl_3$$

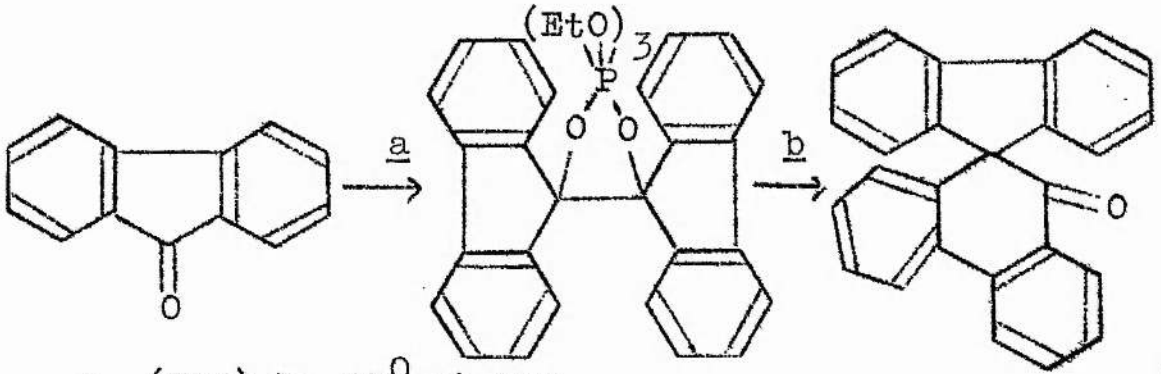
The Michaelis-Arbusov reaction and the Perkov reaction, between tervalent phosphorus reagents and halo- and halo-carbonyl compounds respectively, have been reviewed elsewhere[10] and will not be discussed further here.

The attack of tervalent phosphorus reagents on carbonyl oxygen, again introduced briefly in the 1962 review,[16] has been studied in much greater detail in recent years, and shows a number of parallels with the deoxygenations of nitroso- and nitro-compounds considered later. The phosphorus compound may be involved predominantly as a nucleophile or as an electrophile, depending on the relative importance of lone-pair donation from phosphorus and p_{π}-d_{π} bonding from oxygen.

Reports of the complete removal of oxygen, with the possibility of carbene formation, are not common. However, Arbusov[41] has reported a small yield of stilbene by the reaction of benzaldehyde with triethyl phosphite under reflux, Poshkus and Herweh[42] reported traces of tetraphenylethylene from the corresponding reaction with benzophenone, and Ramirez[42] et al. prepared biphthalyl (11) in reasonable yield from phthalic anhydride:



Such deoxygenations are more often rationalised in terms of stable 1:1 and 1:2 adducts which, by the elimination of the phosphate or phosphine oxide, may give rise to compounds possessing the appropriate degree of unsaturation. Thus Borowitz and Anschel,[44] from the reaction of triethyl phosphite with fluorenone at 25°, isolated 2,2,2-triethoxy-4,5-bisdiphenylene-1,3,2-dioxaphospholane (50%), which, on heating in benzene, rearranged to 9-diphenylene-phenanthrone (12):



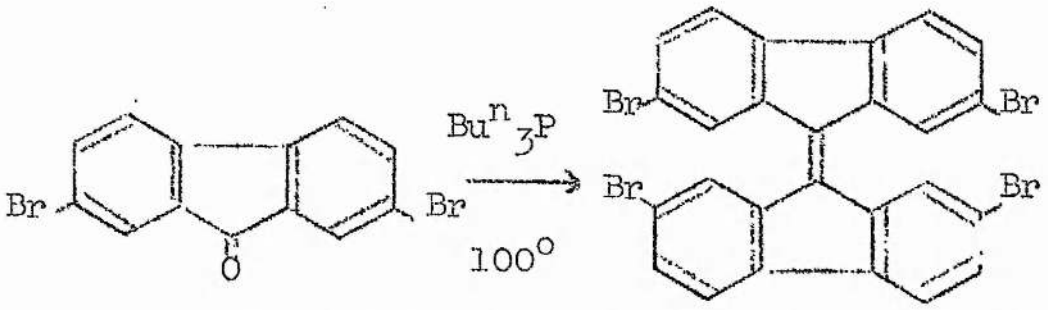
a $(EtO)_3P$, 25°, 24 hrs.

b heat, benzene.

(12)

+ $(EtO)_3PO$

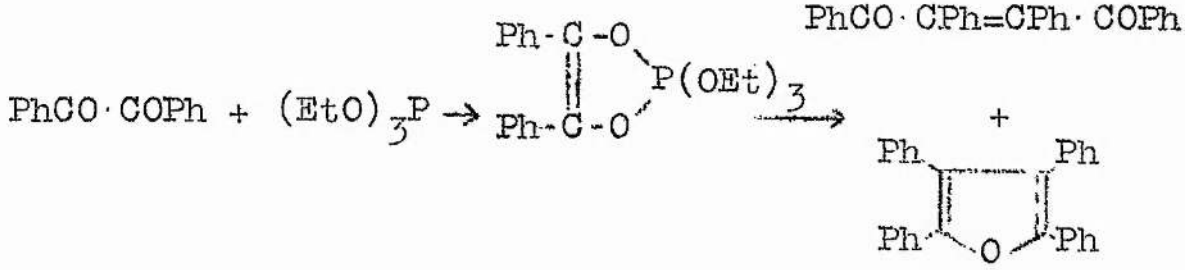
In an excess of triethyl phosphite at 150°, the rearranged product was obtained directly in 74% yield, together with bifluorenylidene (3%). The yield of bifluorenylidene was increased to 40% if tributylphosphine was used, and to 64% if 2,7-dibromofluorenone (13) was used in place of the unsubstituted fluorenone:



(13)

Similar results, with the formation of 1:1 or 1:2 adducts of phosphite or phosphine with the carbonyl compound, have been reported for benzil[45,46], benzoyl cyanide[47], benzoin[48], indanetrione[49,50] and isatins[51], hexafluoroacetone[52], and with a variety of polyketones in a series of investigations by Ramirez and his co-workers.[53-62]

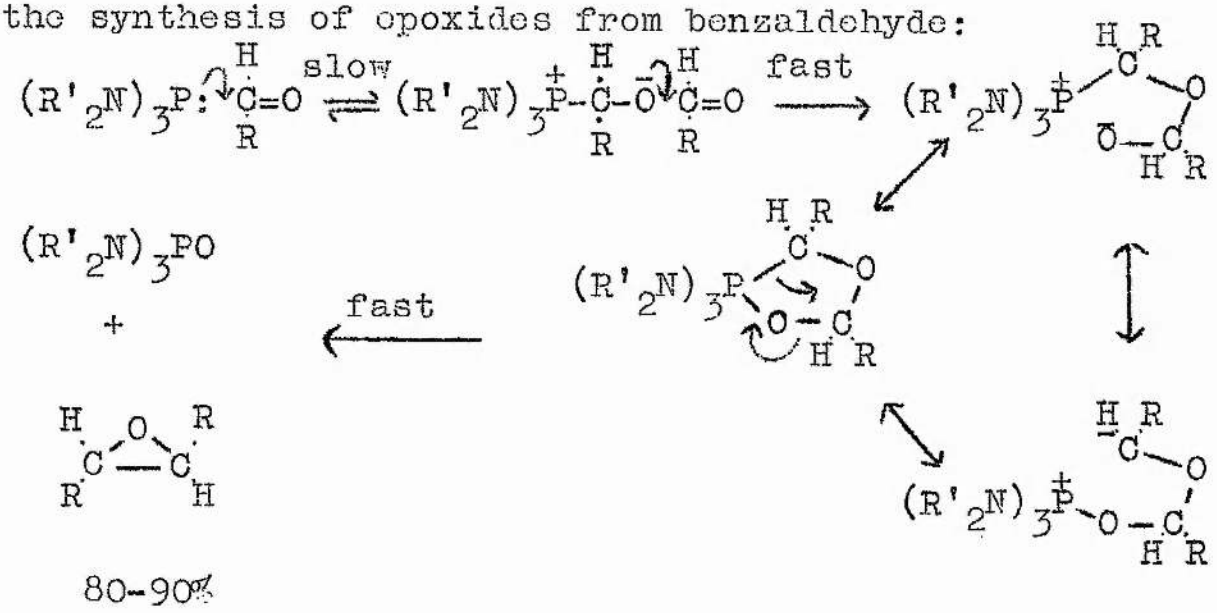
In the case of benzil[45,46] it was shown that the 1:1 adduct with triethyl phosphite decomposed in the presence of cupric sulphate[63] to give cis-dibenzoylstilbene (41%) and tetraphenylfuran (18%):



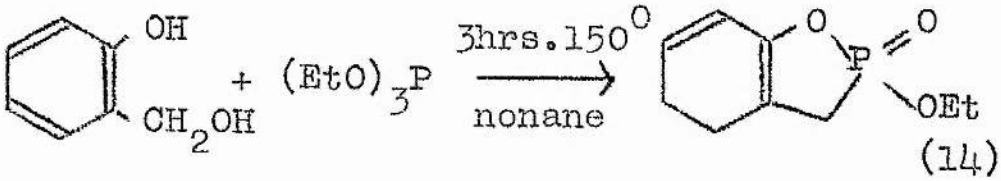
The formation of benzoin derivatives when the decomposition was carried out in various alcohols suggested an intermediate phenyl benzoyl carbene.

Where a stable phospholane has not been isolated,

an open dipolar adduct has been suggested.[54,64] This may be in equilibrium with the cyclic form,[50,54] or may be a hybrid of the two forms as suggested by Mark[65] for the synthesis of epoxides from benzaldehyde:



The formation of 1:1 adducts has also been reported between o-hydroxybenzyl alcohol and trialkyl phosphites[66] (14) and between catechol and dichloromethylphosphine[67] (15):



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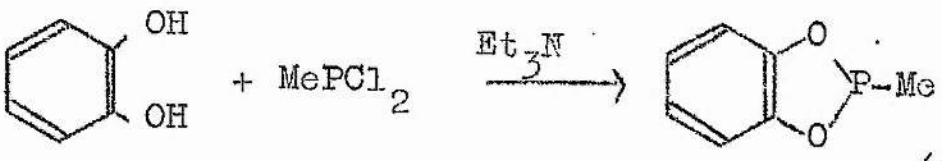


(15)

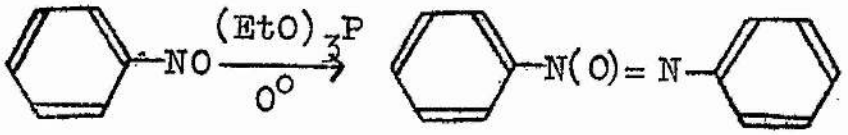
3. Reactions of Nitroso- and Nitro-compounds with Tervalent Phosphorus Reagents.

The reduction of nitroso- and nitro-compounds by tervalent phosphorus reagents has recently been reviewed.[17] Interest in these reactions centres both upon their wide applications in synthesis, and upon the details of the reaction mechanisms, and these two aspects will, therefore, be reviewed in turn here. In addition, the chemistry of the electron-deficient, monovalent nitrogen intermediate, the nitrene, will be discussed briefly in the light of its relevance to the mechanism of many of the deoxygenations now studied.

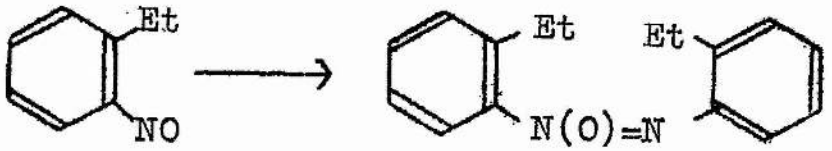
(a) Preparative aspects of the reaction with aromatic nitroso-compounds. Although tervalent phosphorus compounds have been used as reducing agents since 1932,[68] the first tentative report of a reaction with an aromatic nitroso-compound did not appear until 1954, when Hoffmann and Horner,[69] in a reference to unpublished work, stated that substituted nitrosobenzenes, but not nitrosobenzene itself, reacted with triphenylphosphine to give the corresponding azoxybenzenes (16):

$$ArNO + Ph_3P \longrightarrow ArN{=}N(O)Ar + Ph_3PO \qquad (16)$$

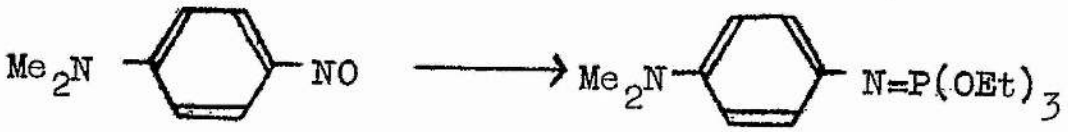
A further seven years elapsed before a systematic investigation commenced.[70-72]



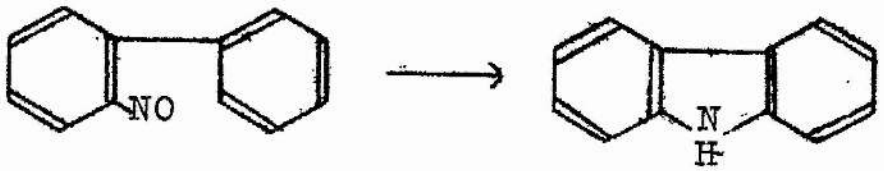
(21%) (17)



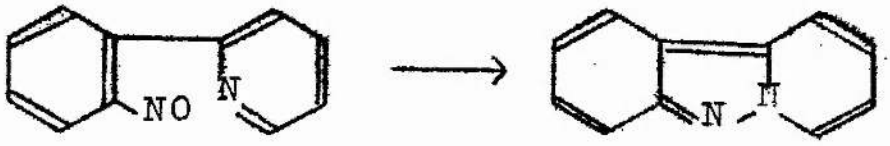
(47%) (18)



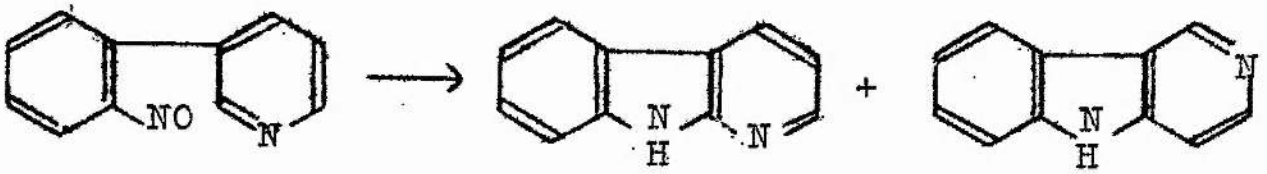
(58%) (19)



(76%) (20)



(98%) (21)

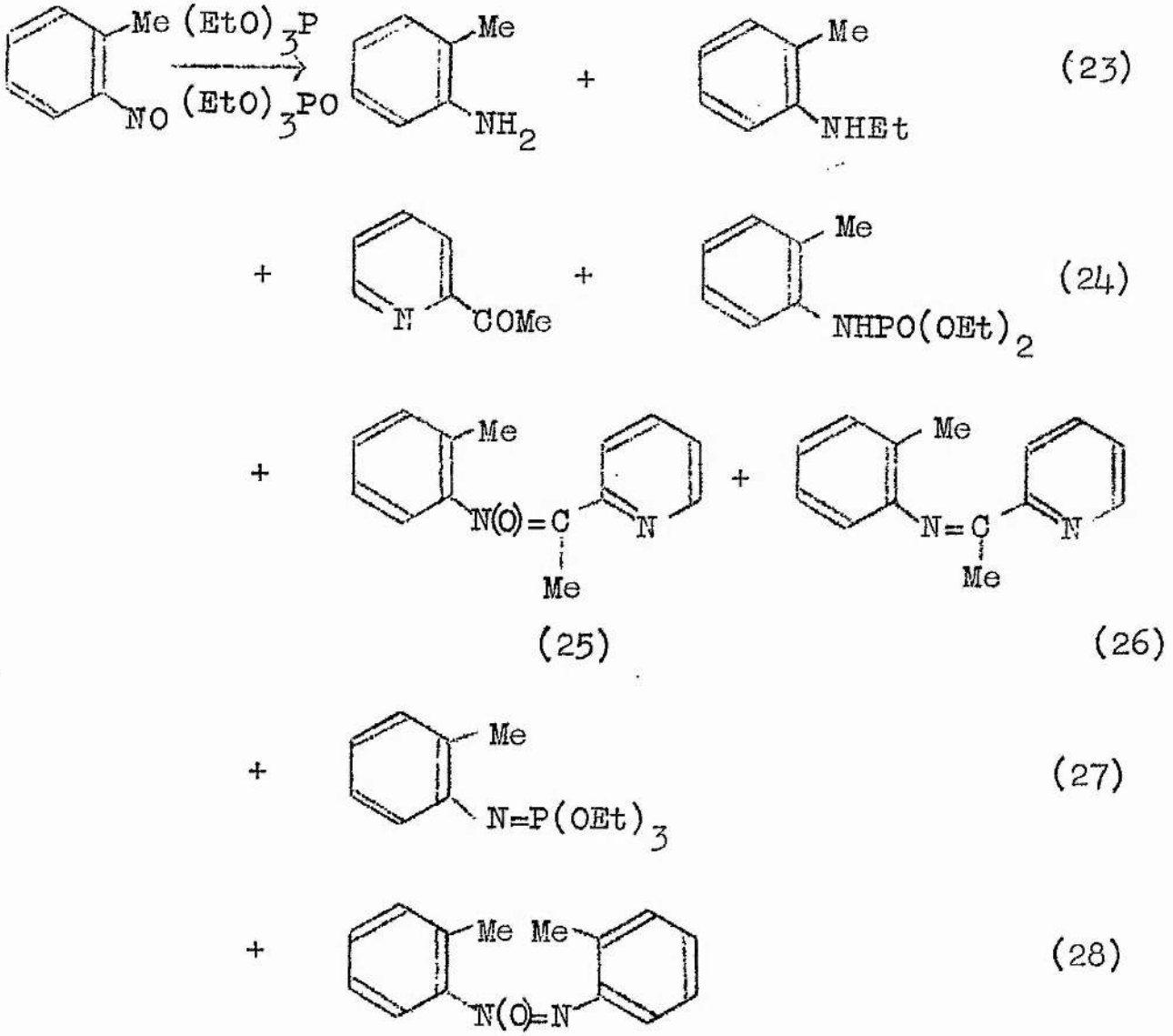


(64% total) (22)

SCHEME 1

Bunyan and Cadogan,[71,72] in their account of the deoxygenation of a series of aromatic nitroso-compounds, laid the foundations for much of the subsequent preparative work and the discussions of mechanism arising from these reactions. Thus from the reaction of triethyl phosphite with nitrosobenzene, o-ethylnitrosobenzene, NN-dimethyl-p-nitrosoaniline, 2-nitrosobiphenyl, and 2- and 3-o-nitrosophenylpyridine, they isolated good yields of azoxybenzene (17), 2,2'-diethylazoxybenzene (18), triethyl N-p-dimethylaminophenylphosphorimidate (19), carbazole (20), and pyrid[1,2-b]indazole (21) and α- and γ-carboline (22), respectively (Scheme 1). These reactions were carried out in a hydrocarbon solution at 0°, with a small excess of triethyl phosphite.

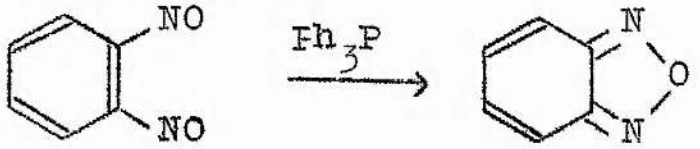
Sundberg[73] in turn investigated the reactions of o-alkylnitrosobenzenes with an excess of triethyl phosphite in triethyl phosphate solution. He was able to recover a number of amines (23) and hydrolysis products (24) in very small yields, together with, in the case of o-nitrosotoluene, a skeletal rearrangement product, N-o-tolyl-α-methyl-α-(2-pyridyl)nitrone (25) and the deoxygenated anil (26). The corresponding trialkyl N-phenylphosphorimidates (27) were also isolated, together with the expected 2,2'-dimethylazoxybenzene (28)


Me
(EtO)3P
NO
(EtO)3PO
Me
NH2
+
Me
NHEt
(23)
+
N
COMe
+
Me
NHPO(OEt)2
(24)
+
Me
N(O)=C
N
Me
+
Me
N=C
N
Me
(25)
(26)
+
Me
N=P(OEt)3
(27)
+
Me
Me
N(O)=N
(28)

SCHEME 2

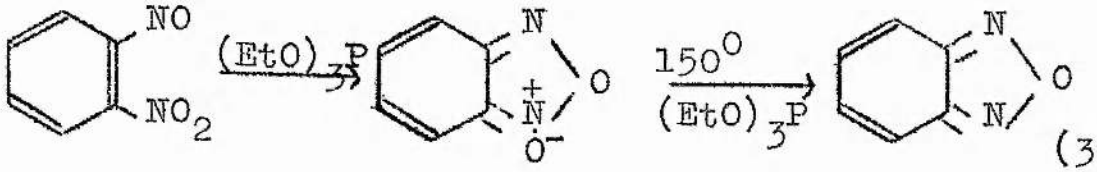
in trace amounts only (Scheme 2).

Boyer and Ellzey[70] described an earlier deoxygenation of an aromatic nitroso-compound in their preparation of benzofurazan (29) from o-dinitrosobenzene:



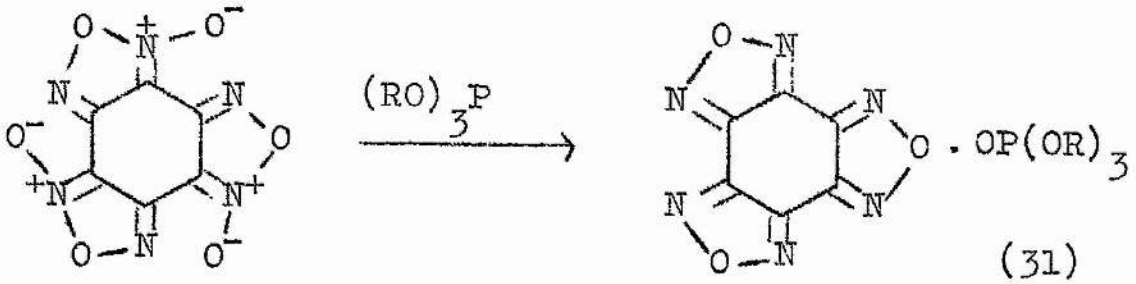
(29)

In a similar fashion, o-nitronitrosobenzene was smoothly reduced by triethyl phosphite to the furazan oxide, which in turn gave the furazan on further reduction under more forcing conditions[74] (30):



(30)

This reaction has been extended by Bailey and Evans,[75,76] and by Cameron and Prout,[77] to the corresponding reductions of benzotrifuroxan to benzotrifurazan (31), and to the formation of high-melting adducts with triphenylphosphine (32).



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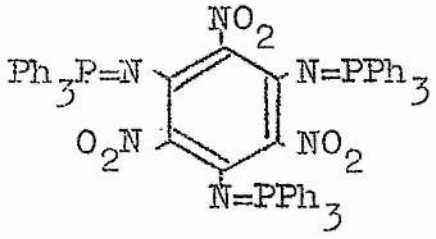


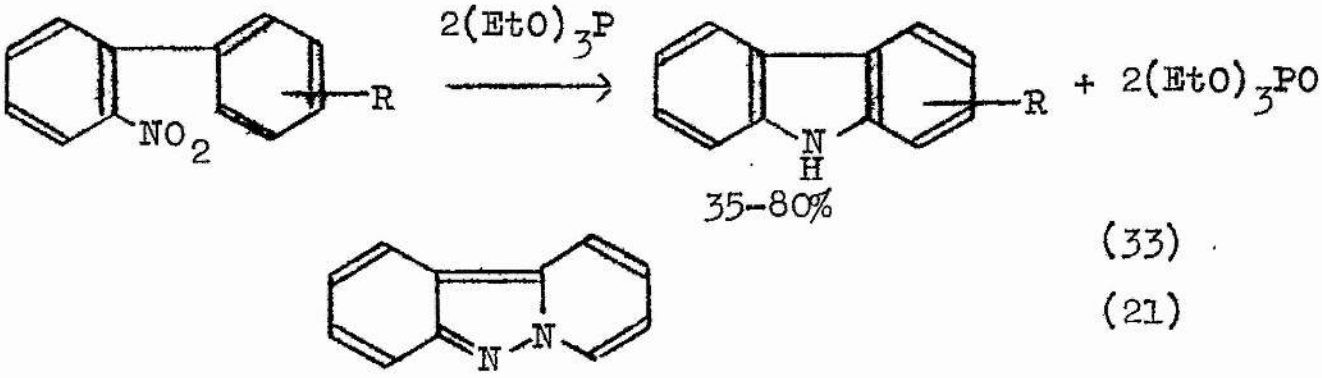
(32)

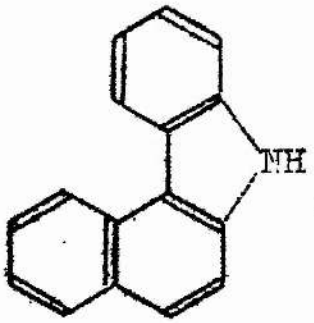
Finally, Burdon, Morton and Thomas[75] have described the preparation of a range of perfluoro azo-, azoxy- and hydrazobenzenes from the related nitroso-compounds and triethyl phosphite:

$$RC_6F_4NH_2 \xrightarrow{HCOOOH} RC_6F_4NO \xrightarrow{(EtO)_3P} RC_6F_4N(O)=NC_6F_4R$$

The main limitation to the scope of the reaction between tervalent phosphorus reagents and aromatic nitroso-compounds as a preparative method lies, however, in the difficulty sometimes encountered in the preparation of the required nitroso-compound from the corresponding nitro- or amino-compound.

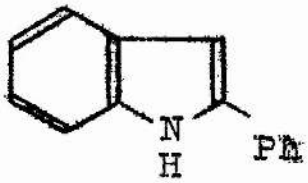
(b) Preparative aspects of the reaction with aromatic nitro-compounds. This difficulty in the preparation of the starting material was overcome by repeating the deoxygenations with the more readily available nitro-compounds. Cadogan and co-workers[74,79] reported the synthesis of a number of substituted carbazoles (33) from the reaction of the corresponding 2-nitrobiaryls,





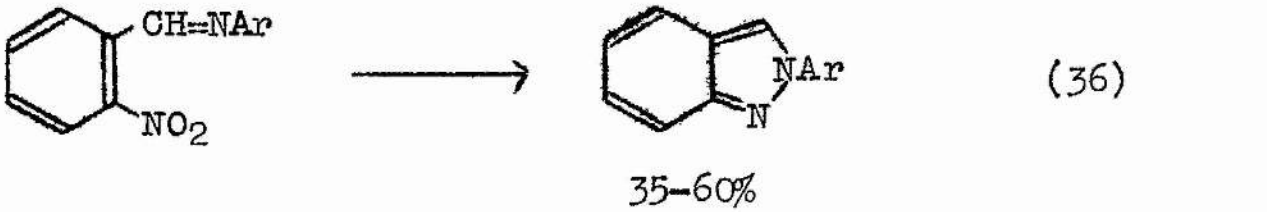
(34)

64%



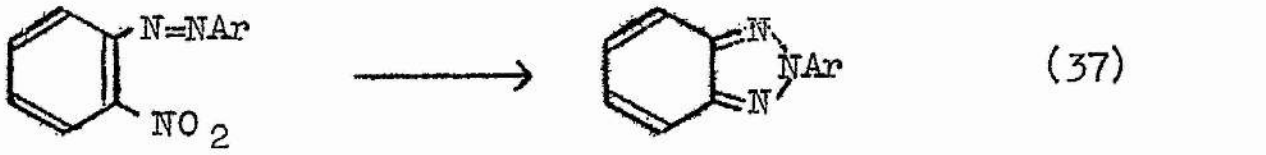
(35)

58-85%



(36)

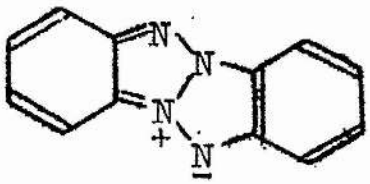
35-60%



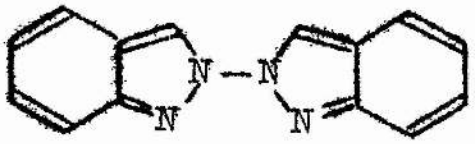
(37)

30-70%

SCHEME 3



(38)



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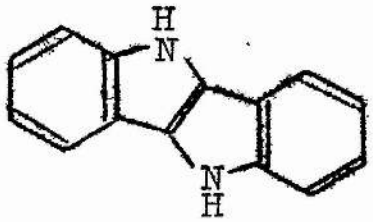


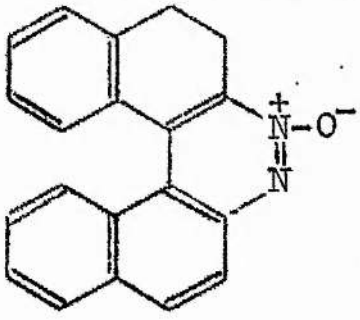
(40)

SCHEME 4

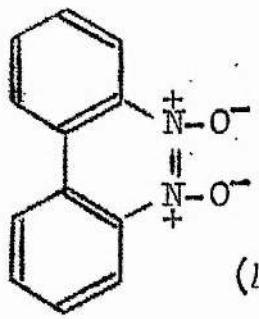
and of pyrid[1,2-b]indazole (21) from 2-o-nitrophenylpyridine, with triethyl phosphite. In a like manner, 3,4-benzocarbazole (34) was prepared from 1-o-nitrophenylnaphthalene, 2-phenylindole (35) from cis- and trans-2-nitrostilbene, 2-arylindazoles (36) from 2-nitrobenzylideneanilines and 2-aryl-2H-benzotriazoles (37) from 2-nitroazobenzenes (Scheme 3).

The reaction of triethyl phosphite with suitable dinitro-compounds led to polycyclic compounds containing fused five-membered rings, dibenzo[b,f]-1,3a,4,6a-tetra-azapentalene (38), 2,2'-bi-2H-indazolyl (39), and indolo[3,2-b]indole (40) being obtained from 2,2'-dinitroazobenzene, o-nitrobenzaldehyde azine, and 2,2'-dinitrostilbene respectively (Scheme 4).

The use of phosphine in ethanolic alkali[80,81] has been reported as an alternative to triethyl phosphite. Thus Bellaart[80] used this reagent to prepare benzo[f]-naphtho[2,1-c]cinnoline-N-oxide (41) and benzo[c]-cinnoline-N,N'-dioxide (42) from 2-nitronapthalene and 2,2'-dinitrobiphenyl respectively.

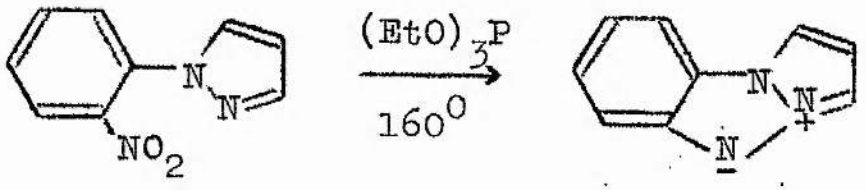


(41)



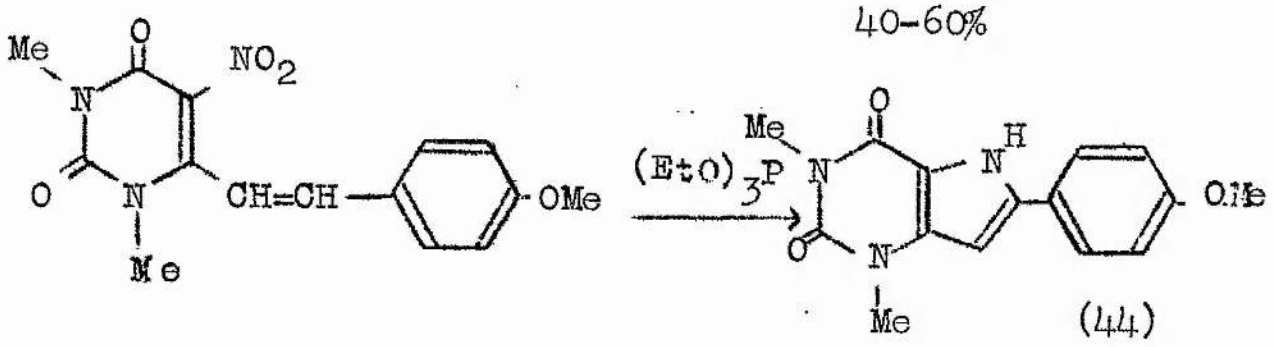
(42)

The synthesis of another series of benzotriazoles[82] and of a number of pyrrolo-pyrimidines[83] has been described. Pyrazolo[1,2-a]benzotriazole (43) was obtained in good yield from 1-o-nitrophenylpyrazole while reduction



(43)

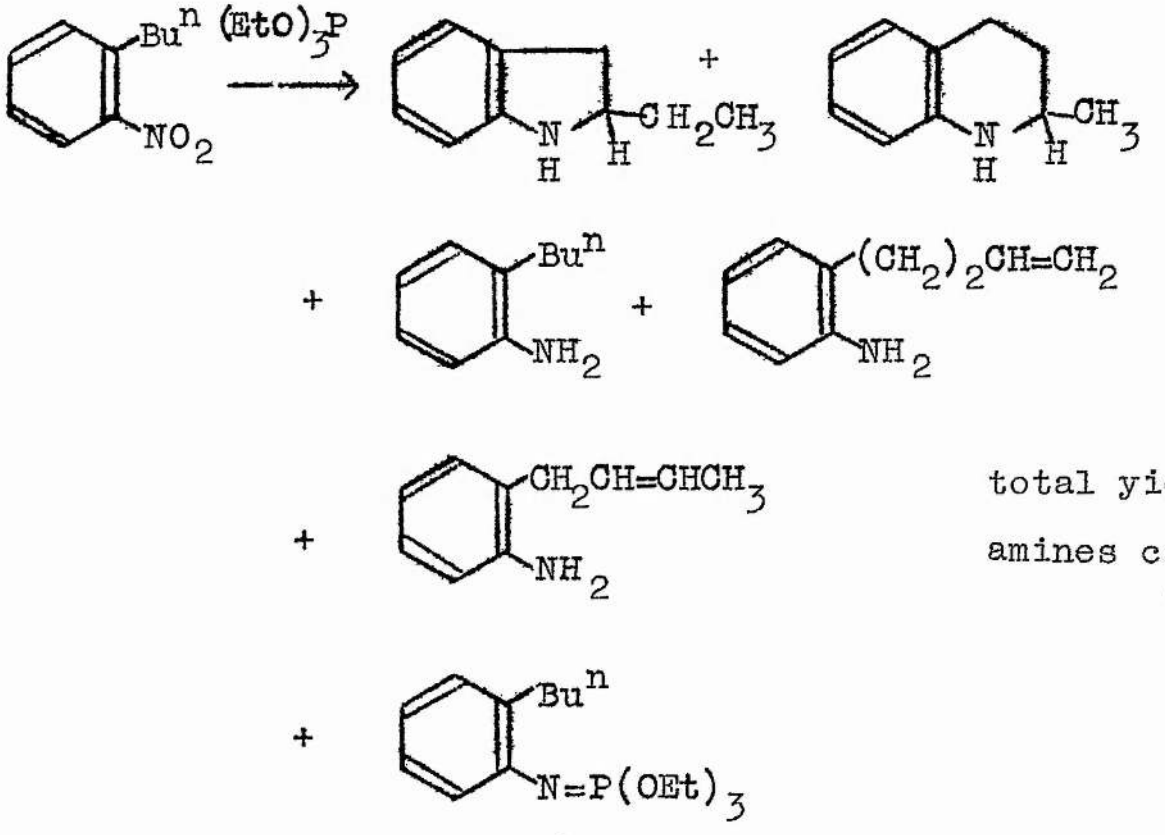
and cyclisation of 1,3-dimethyl-5-nitro-6-p-methoxystyryluracil gave the corresponding pyrolo[3,2-d]-pyrimidine (44)



(44)

In the latter case, irradiation of the reaction mixture with ultra-violet light for 14 hours gave a low yield of the same product; however it is not certain that the reaction mixture was maintained at 0° and therefore there may have been a thermally induced effect in addition to any photochemical reaction.

While the present investigation was in progress, Sundberg examined, in greater detail, the deoxygenation



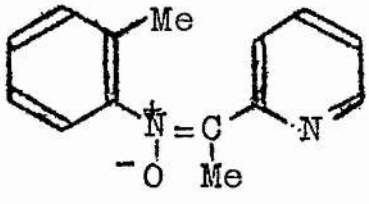
(45)

(46)

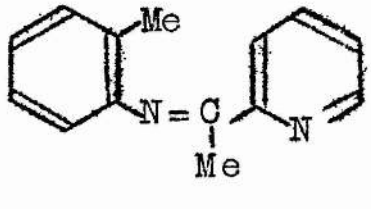
total yield of amines ca. 9%

(47)

ca. 40% total yield



(25)

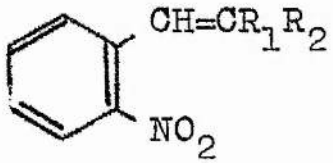


(26)

SCHEME 5

of o-alkylnitrobenzenes by triethyl phosphite[73,84,85] and extended the synthesis of substituted indoles from o-nitrostyrene,[86-88] described earlier.[74] In the reaction of o-butylnitrobenzene with triethyl phosphite he reported the isolation of a number of cyclised products (45) and other amines (46), in addition to the expected N-o-butylphenylphosphorimidate (47), although there was no evidence for rearrangement products of the type found with o-nitrosotoluene (25,26). N-o-tolyl-2-acetimidylpyridine (26) was however isolated (37%) from the irradiation of o-nitrotoluene in the presence of a large excess of triethyl phosphite at room temperature (Scheme 5). Irradiation of o-nitrobiphenyl and cis- and trans-2-nitrostilbene in triethyl phosphite gave carbazole and 2-phenylindole respectively.

The deoxygenation of four β,β-disubstituted o-nitrostyrenes (48-51) was described in full.



$R_1, R_2 = (CH_2)_5$ (48)

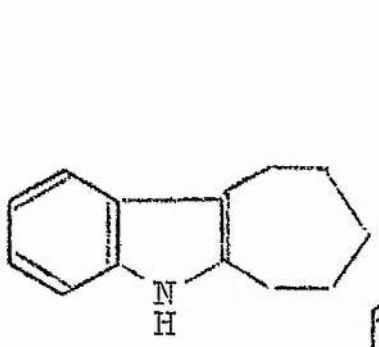
$R_1, R_2 = (CH_2)_4$ (49)

$R_1 = R_2 = CH_3$ (50)

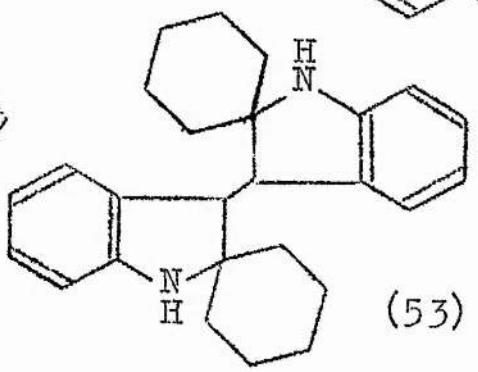
$R_1 = Ph,\ R_2 = CH_3$ (51)

Thus cyclohexylidene(o-nitrophenyl)methane (48) gave as the major product 2,3-pentamethyleneindole (52,25%). In addition, 3',3'''-bispiro[cyclohexane-1,2'-indoline],

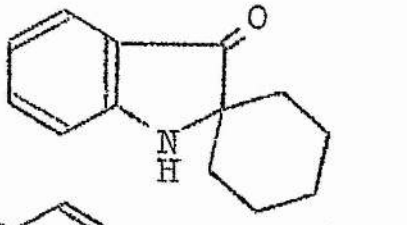
(53, 24%), and spiro [cyclohexane-1, 2'-indolin-3'-one], (54, 8%), were isolated.



(52)

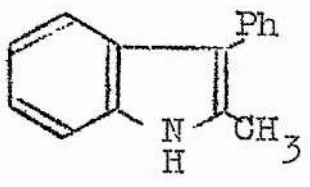


(53)



(54)

The cyclopentylidene compound (49) gave only a low yield of 1,2,3,4-tetrahydrocarbazole (15%), the analogue of the indole (52), but β,β-dimethyl-o-nitrostyrene (50) gave products corresponding to all those described above. α-Methyl-2'-nitrostilbene (51), however, underwent deoxygenation with rearrangement, in high yield, to the indole (55, 75%), although no bi-indoline or indolinone were detected. In addition to the major product 2-methyl-3-phenylindole (55), 1-ethyl-2-methyl-3-phenylindole (56, 21%) was formed, presumably by ethylation of the indole (55) by triethyl phosphate.



(55)

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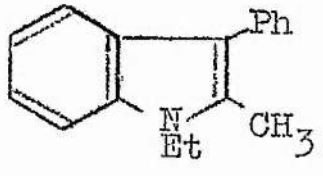
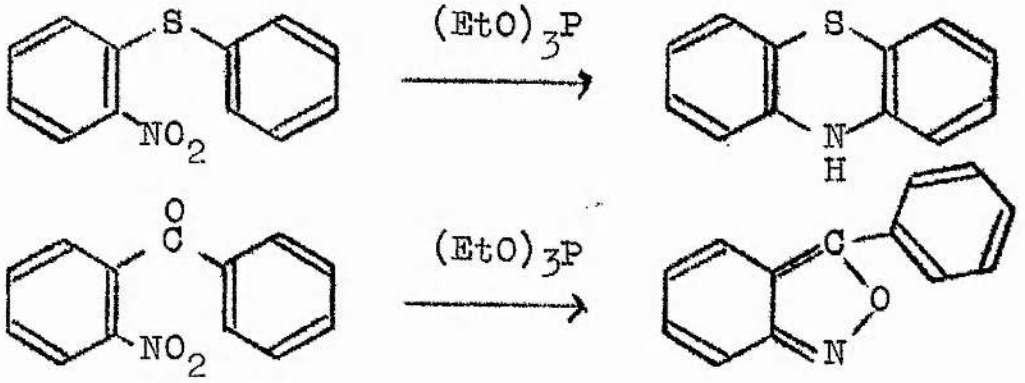
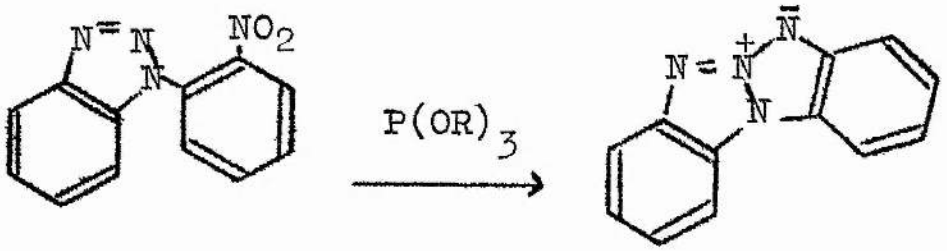


(56)

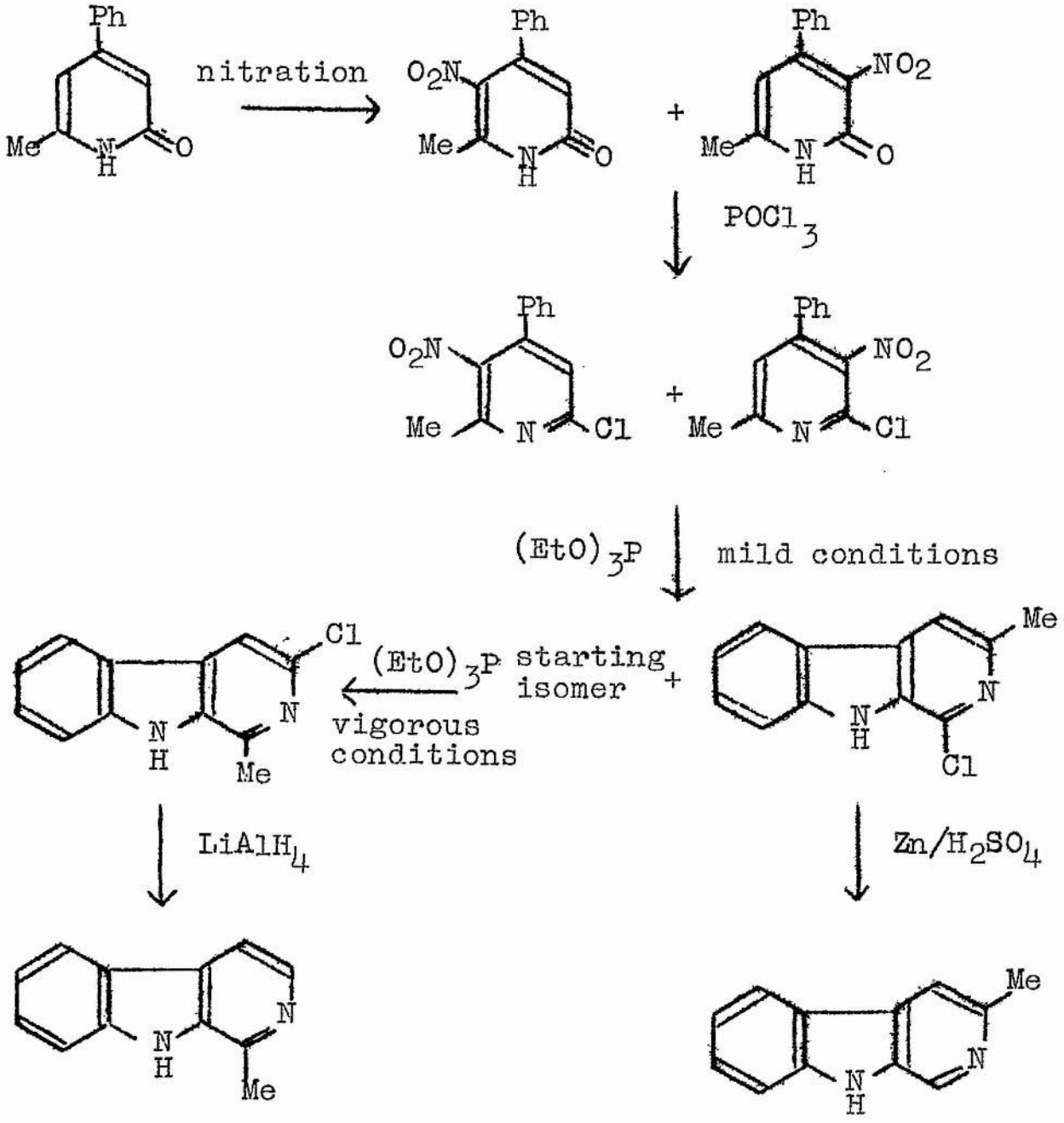
Further advances in the scope of the deoxygenation reaction were made by Cadogan, Mackie and Todd[89] in their report of the synthesis of phenothiazine (54%) from 2-nitrophenyl phenyl sulphide, and of 3-phenylanthranil (58%) from 2-nitrobenzophenone:



Ring closure with tervalent phosphorus reagents also proved superior both to the earlier decomposition of azido-compounds, and to nitro-group reduction by ferrous oxalate, for the formation of tetra-azapentalenes from the corresponding nitro-triazoles;[90] thus 1-(o-nitrophenyl)-1H-benzotriazole gave dibenzo[b,f]-1,3a,6,6a-tetra-azapentalene (57,60-90%), (cf. 45% by azide decomposition).

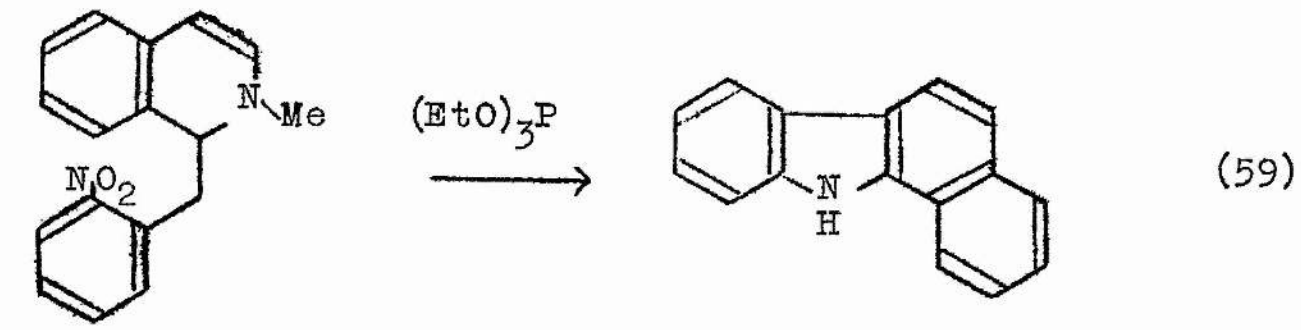


(57)

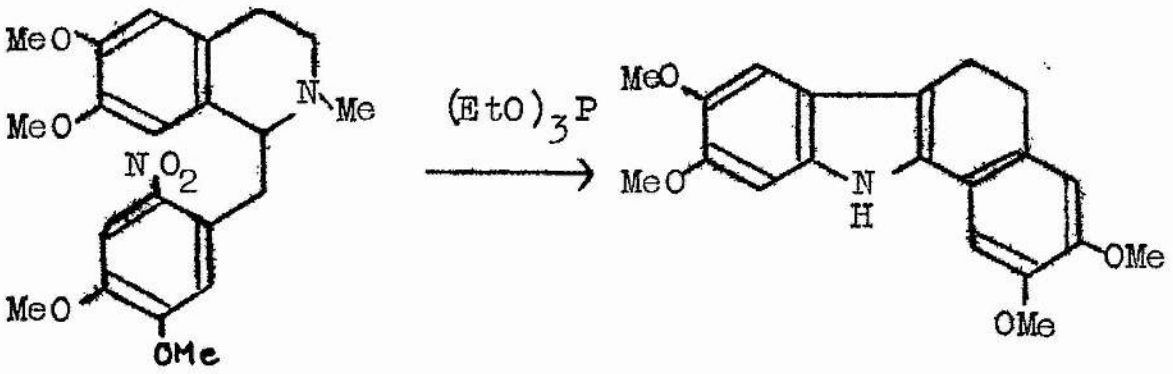


harman (58)

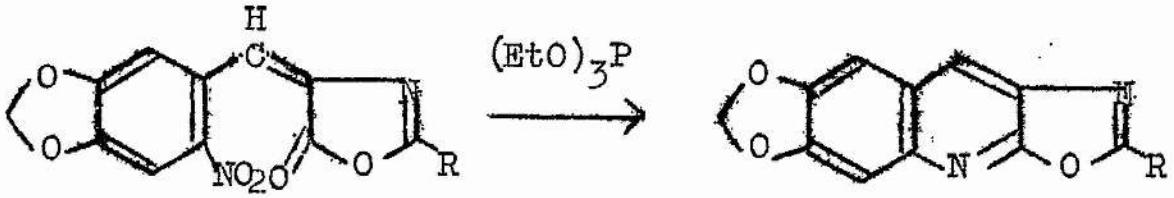
SCHEME 6



(59)



(60)



(61)

SCHEME 7

Very recently, the alkaloid harman (58) has been synthesised from 6-methyl-4-phenyl-2-pyridone[91] with the aid of triethyl phosphite (Scheme 6). The same authors[92] also report novel syntheses of benzo[α]-carbazoles (59,60) and oxazolo[5,4-b]quinoline ring systems (61) from the appropriate aromatic nitro-compound and triethyl phosphite (Scheme 7).

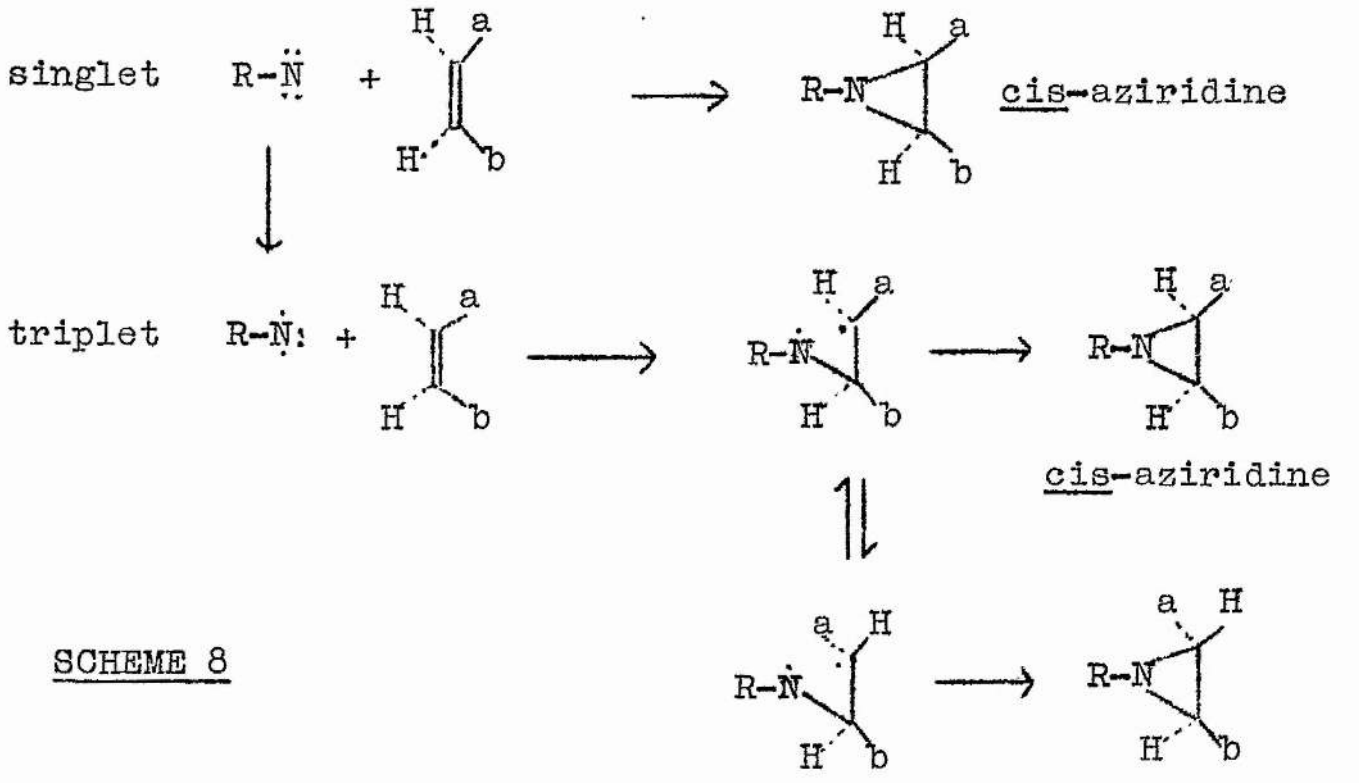
(c) The development of the nitrene hypothesis The monovalent nitrogen intermediate R-$\ddot{\underset{\cdot\cdot}{N}}$, where R may be hydrogen, a halogen, an alkyl, an aryl, a sulphonyl, a phosphazyl or an amino group, is isoelectronic with the carbene[93] R-$\ddot{C}$H and the monovalent oxygen cation[94] R-$\ddot{\underset{\cdot\cdot}{O}}^{+}$. Its existence was first suggested by Stieglitz[95] in 1914 to account for the mechanisms of the Hofmann, Curtius, Lossen and Beckmann rearrangements. Although recent work by Robson and Speakman[96] has cast doubts on the participation of a discrete nitrene in the thermal (Curtius) rearrangement of acyl azides to isocyanates, the existence of the nitrene, under a variety of names, has, in general, been accepted as a useful hypothesis. As such, it has been fully reviewed up to 1964.[97-99]

Recent work has concentrated on the determination of the electronic structure of the species by an examination of its chemical and physical behaviour under different

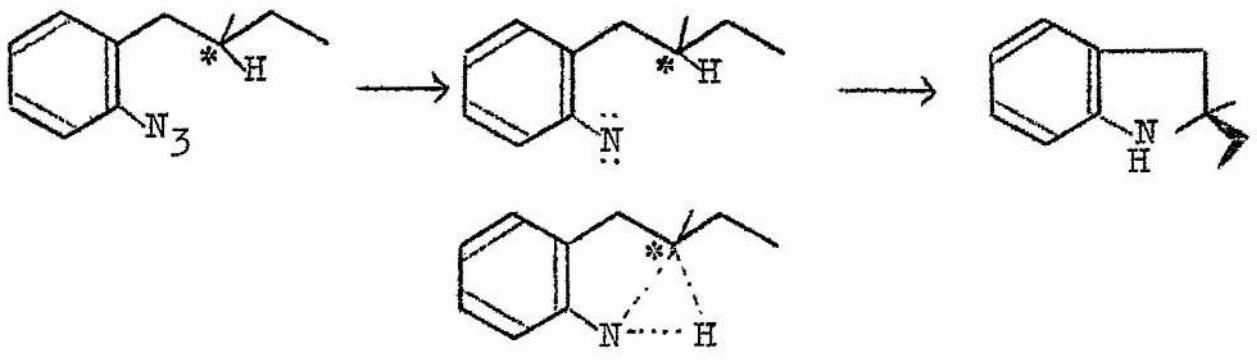
conditions. The nitrene can, in theory and in practice, exist either in the singlet or triplet state. In the singlet state, $-\ddot{\underset{\cdot\cdot}{N}}$, with all electrons paired, the nitrene would be highly electrophilic and would add stereospecifically to double bonds. In the triplet state, $-\dot{N}:$, with two unpaired electrons, the behaviour would be that of a biradical, showing non-stereospecific additions, and insertions into different bonds.

Theoretical calculations,[100] e.s.r. spectra,[101,102] and ultra-violet absorption spectra,[103-105] usually at 77°K in a variety of organic glasses, indicate that photolytically generated nitrenes exist in a triplet ground state. Reiser[105] suggested that the reactive species in the photolytic cyclisation of 2-azidobiphenyl to carbazole might be an excited triplet but admitted that "while the existence of the nitrene intermediate seems established, its spin state in the reactions must still remain in doubt". The relevance of the information gained from photolysis in a solid matrix at 77°K to more usual reaction conditions must also be questioned.

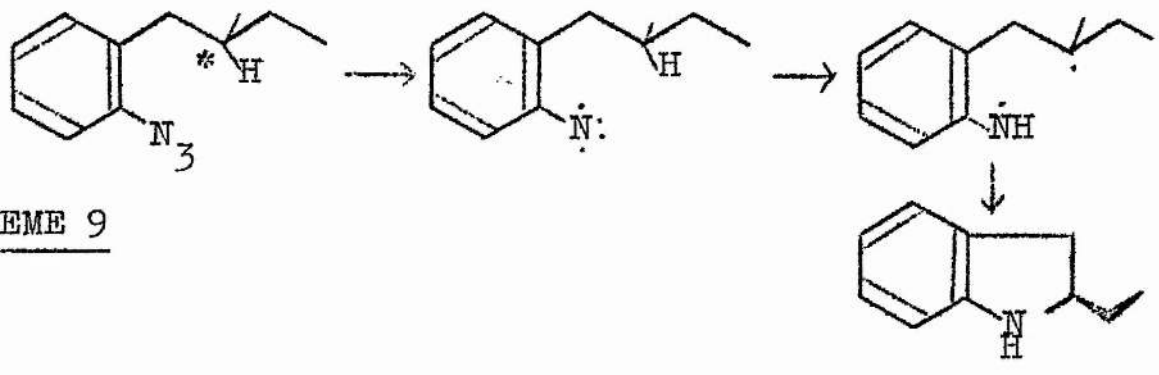
The chemical evidence, based on the variations in product structure with reagent concentration, suggests that the thermal decomposition of an azide leads to an



SCHEME 8



(62)

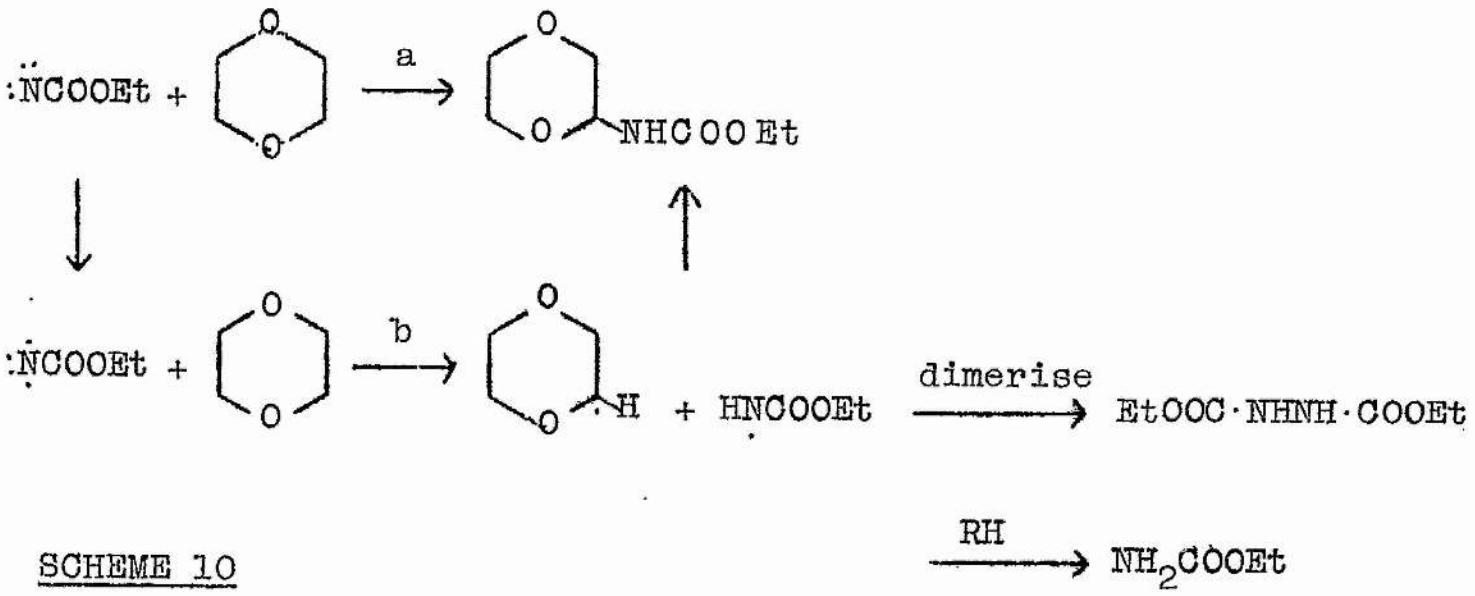


SCHEME 9

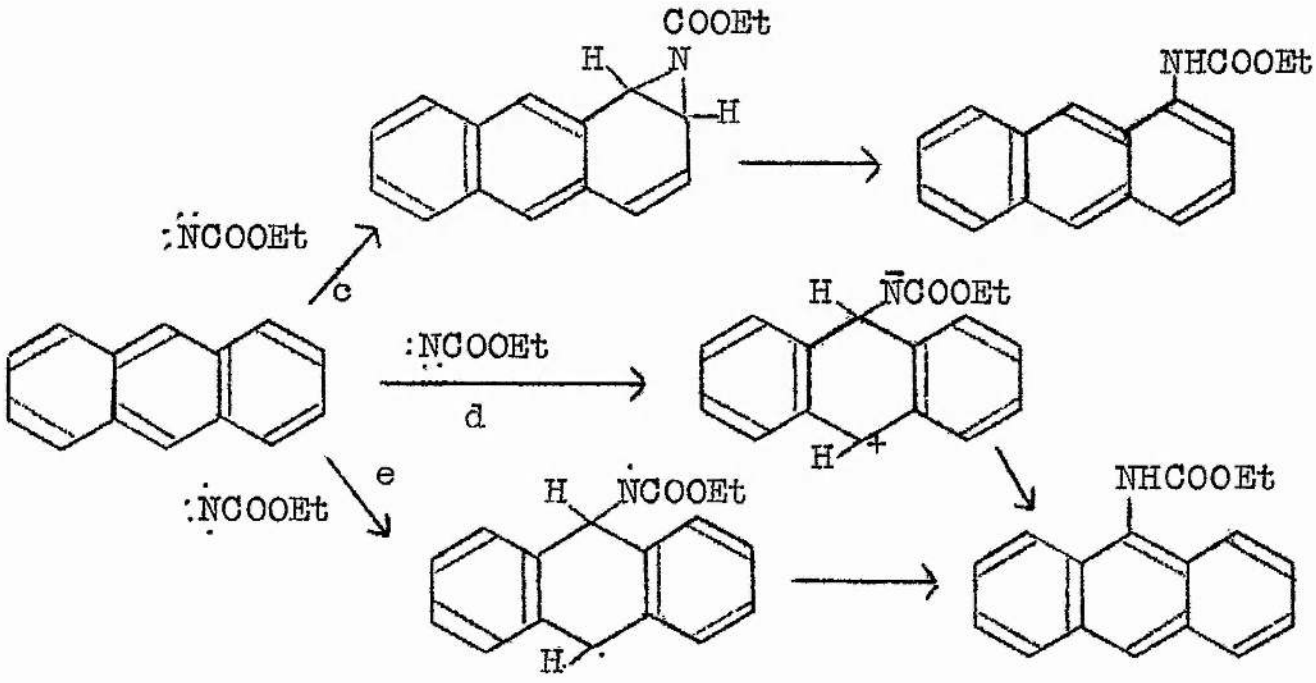
(63)

excited singlet nitrene which may react as such or may decay to the triplet ground state. Lwowski[106] has provided semi-quantitative data from the reaction of carbethoxynitrene, generated by α-elimination from N-(p-nitrobenzenesulphonyloxy)urethan, $O_2N \cdot C_6H_4 \cdot SO_2O \cdot NHCOOEt$, with α-methylstyrene, to show that the decay of the singlet nitrene to the triplet state is about one-thirtieth as fast as the addition to the cis-olefin (Scheme 8).

Smolinsky[107] examined the thermal decomposition of optically-active 2-azido-(2'-methylbutyl)benzene in the vapour phase, and in diphenyl ether solution. In both cases, the major product was optically-active 2-ethyl-2-methyindoline (50% and 43% respectively), which, he suggested, had been formed by direct insertion of a singlet nitrene into the aliphatic C-H bond at the 2-position of the side chain (Scheme 9). The reaction was more likely to involve a partially bonded transition state (62), than to go by the alternative radical abstraction and recombination process which would lead to extensive racemisation (63). A significantly greater degree of retention of configuration was observed in the vapour phase reaction, suggesting that collisional deactivation of the singlet nitrene, possibly followed by reaction



SCHEME 10



SCHEME 11

according to the recombination process (63), took place more readily in solution.

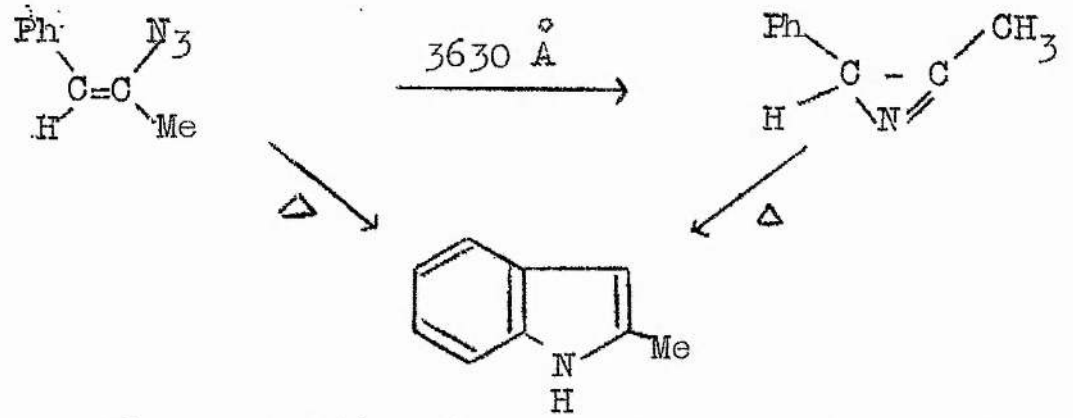
A similar collisional deactivation process was discussed by Anastassiou[108] in relation to the insertion reactions of thermally generated cyanonitrene (64).

$$N_3CN \xrightarrow{\Delta} \ddot{N}CN \xrightarrow{RH} RNHCN$$

In the absence of solvent, insertion took place in an essentially stereospecific fashion, while in an inert solvent such as methylene chloride or bromide, the triplet ground-state became accessible through collisional deactivation, and insertion became non-stereospecific.

The insertion reactions of carbethoxynitrene with 1,4-dioxan,[109] and with anthracene,[110] (Schemes 10 and 11), gave qualitatively similar results. In the former, with varying concentrations of reagent, product ratios suggested that path a predominated over path b in the ratio 3:1. In the latter, a dichotomy of mechanism was again suggested, involving both direct substitution and intermediate aziridine formation. It was also possible that the singlet nitrene might substitute via a zwitterionic intermediate (path d). At high reagent concentrations, paths c, d and e were involved, whereas at low reagent concentrations, path e predominated.

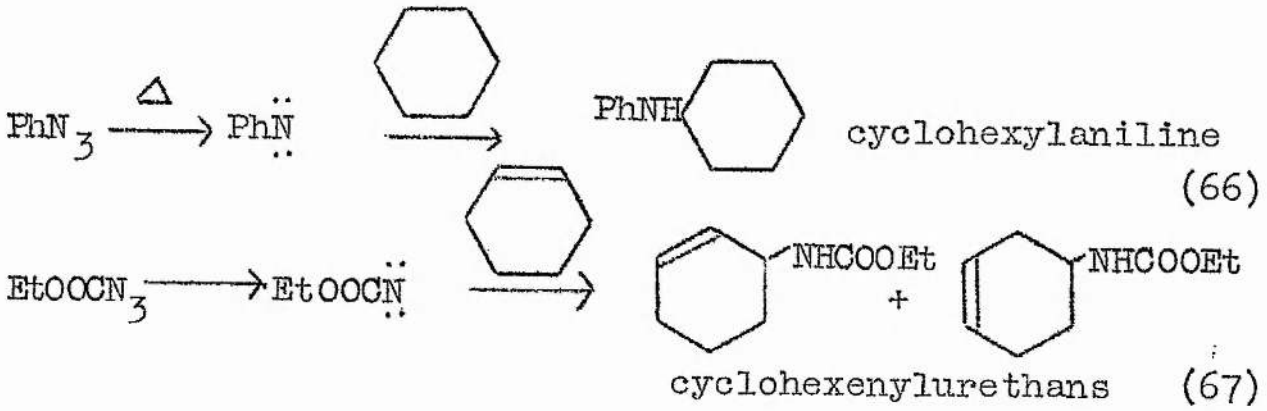
Aziridines and azirines, the chemistry of which has been reviewed by Fanta,[111] have now been isolated from a number of nitrene-olefin addition reactions.[106,110,112-118] Thus while the pyrolysis of β-methyl-β-azidostyrene gave the corresponding indole in 80% yield, irradiation at 3650 Å gave 2-phenyl-3-methyl-2H-azirine (64) as a stable product which, on heating, underwent rearrangement to 2-methylindole[118] (65):



(64)

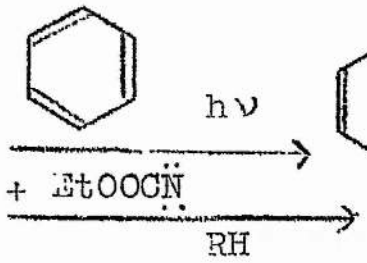
(65)

Where addition to a double bond is not favoured, the nitrene may undergo insertion into a C-H bond (66,67), or into a C-C bond (68), or may abstract hydrogen atoms from the solvent or from other reactants (69). Polymerisation to intractable tars may accompany these reactions.[119]



(66)

(67)



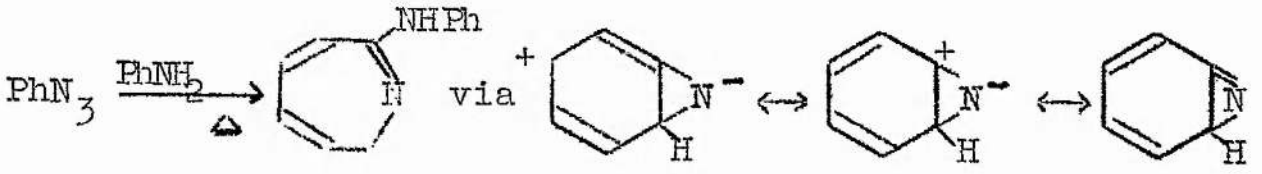
N-COOEt N-carbethoxyazepine (68)

$EtOOCNH_2$ (69)

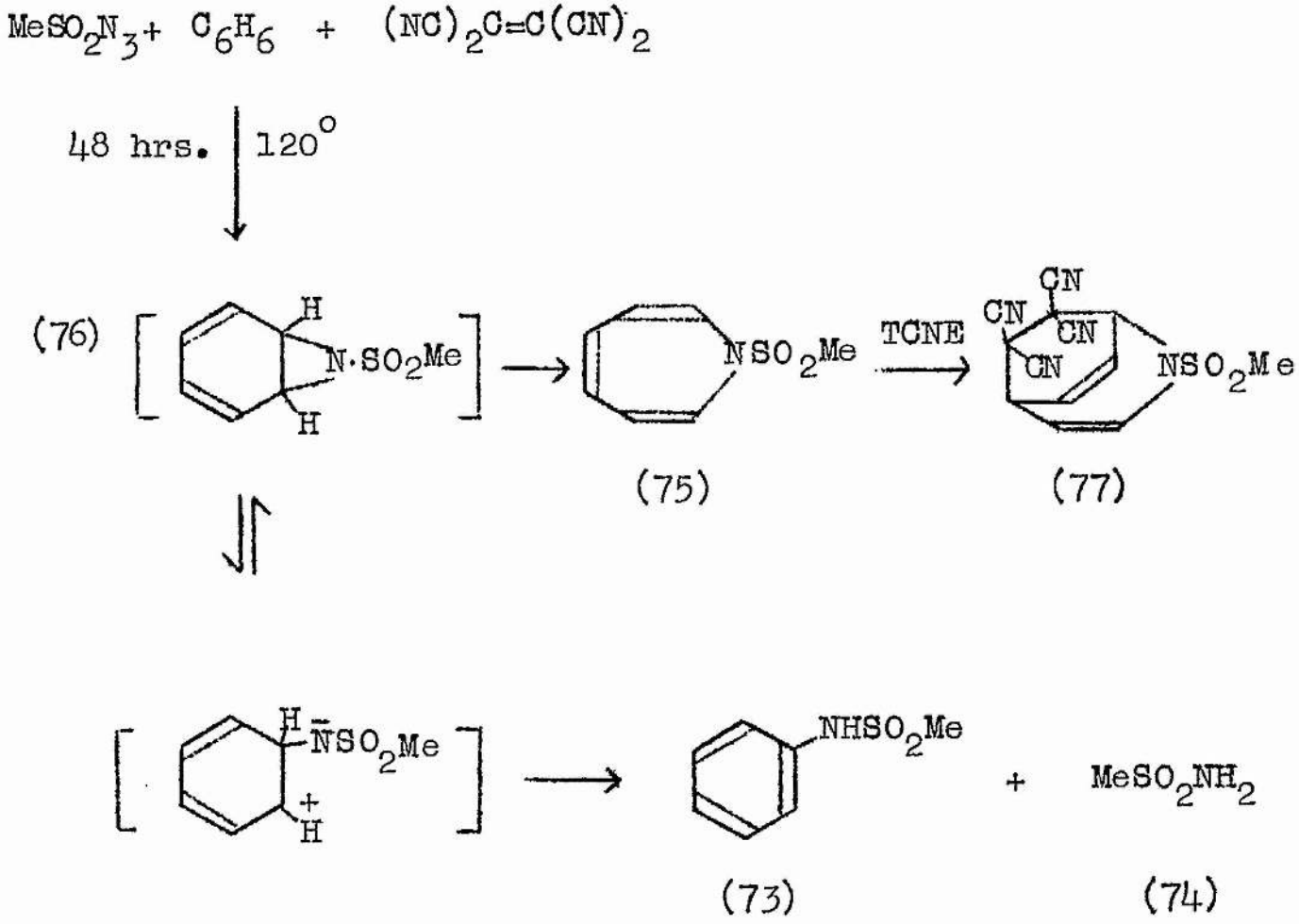
The products from these different, possible, reactions (anilines from phenyl nitrene[118,123] and urethans from carbethoxynitrene,[110,112,120-122] azepines,[107,119-122] and substituted amines by hydrogen abstractions[109,114]) have all been isolated in reasonable yields. Dimerisation, following hydrogen abstraction, may also take place:[109]

$$R\text{-}\ddot{N}\cdot \longrightarrow R\text{-}\ddot{N}\text{-}H \longrightarrow R\text{-}NH\text{-}NH\text{-}R$$

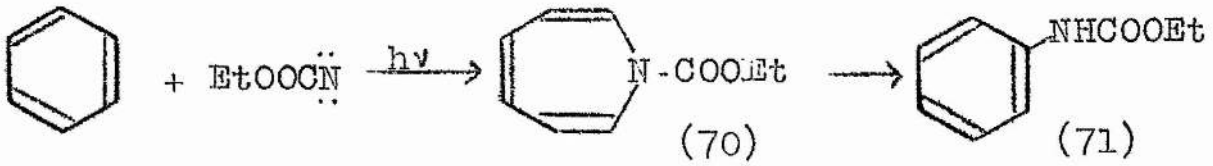
Many different azepines have been investigated in recent years, following the work of Huisgen,[125-126] in 1958, on the decomposition of aryl azides in aniline:



This azepine had been isolated earlier by Wolff,[124] who assigned an incorrect structure to it, and called it "dibenzamil". N-carbethoxyazepine (70), formed in the direct photolytic reaction of benzene with a singlet nitrene,[122] could, it was suggested, then rearrange to the corresponding urethan[120,122] (71).

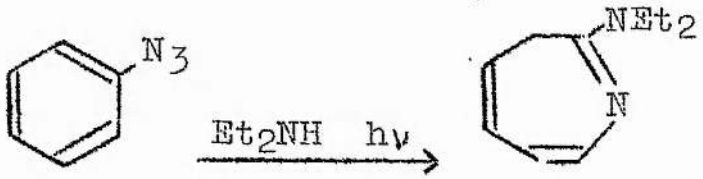

MeSO2N3 + C6H6 + (NC)2C=C(CN)2
48 hrs. | 120°
(76)
H
N·SO2Me
H
NSO2Me
(75)
TCNE
CN
CN
CN
CN
NSO2Me
(77)
H
NSO2Me
+
H
NHSO2Me
(73)
+
MeSO2NH2
(74)

SCHEME 12



(70) (71)

The photolysis of phenyl azide in diethylamine led directly to 2-diethylamino-3H-azepine[119] (72, 34%):

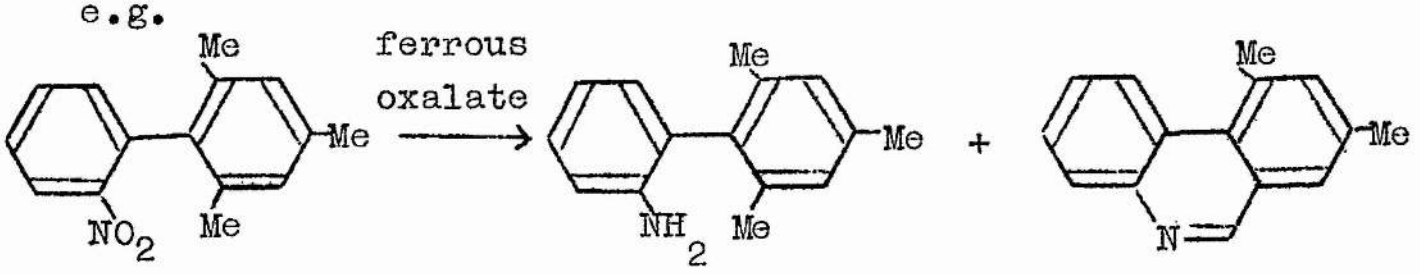


(72)

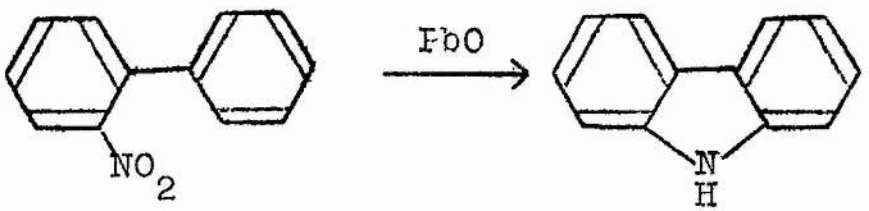
The most recent discussion of the aziridine-azepine system concerned the mechanism of the reaction of methanesulphonylnitrene with benzene.[127] Previous investigations of the thermal decomposition of methanesulphonylazide in benzene had shown the formation of N-methanesulphonylaniline (54%, 73) and methanesulphonamide (14.4%, 74) (Scheme 12). No seven-membered ring compounds (75) were detected. The results were rationalised in terms of a singlet sulphonylnitrene $RSO_2\ddot{N}$ which added to benzene to form the bicyclic aziridine intermediate (76). In an attempt to trap this aziridine, the reaction was repeated at 120° in an excess of tetracyanoethylene (TCNE), to give a non-symmetrical adduct (77) obtained also from an authentic sample of N-methanesulphonylazepine with TCNE in benzene at 80°.

Finally, and under very different reaction conditions,

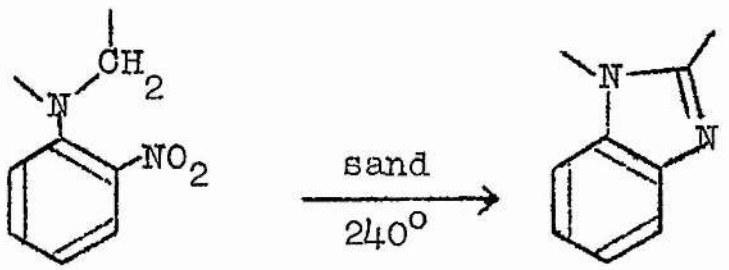
e.g.



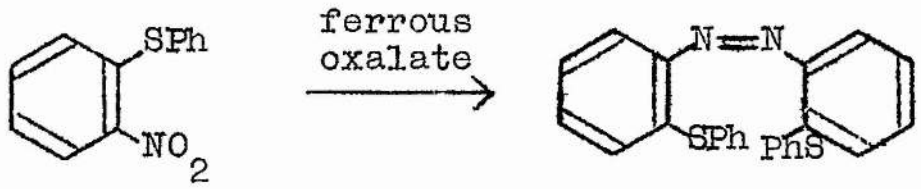
22%



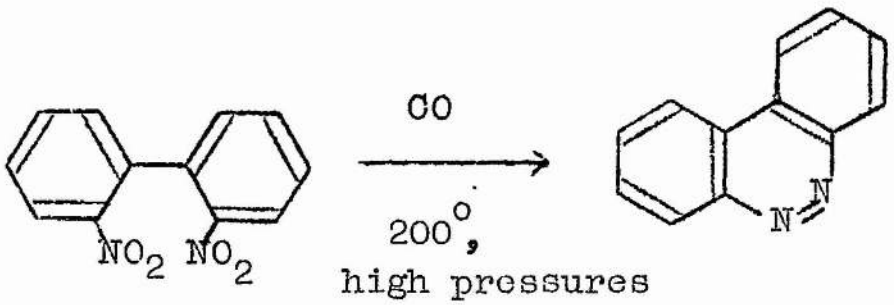
46%



8–88%



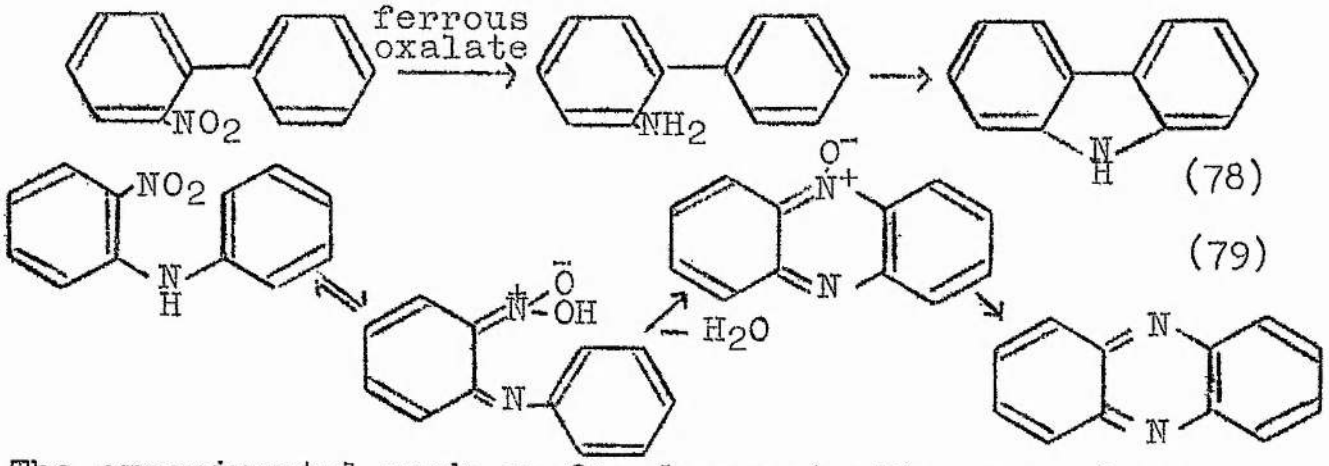
60%



15.5%

SCHEME 13

nitrene formation has been postulated in connection with the thermal cyclisation of aromatic nitro-compounds with ferrous oxalate,[128-131] other metallic catalysts,[131] with sand,[122,133] and with carbon monoxide[134] to give carbazoles, imidazoles, phenazines, phenanthridines, azo- and azoxybenzenes and like compounds, identical with those produced by deoxygenation of the corresponding nitro-compounds with triethyl phosphite, as described earlier (Scheme 13). Alternative reaction mechanisms which do not require the participation of a nitrene intermediate have been proposed; these include the prior reduction of the nitro-group to the amine, which, in the case of 2-aminobiphenyl,[135] is known to undergo ring closure (78), and the dehydration of the aci-nitro form[132,133](79):

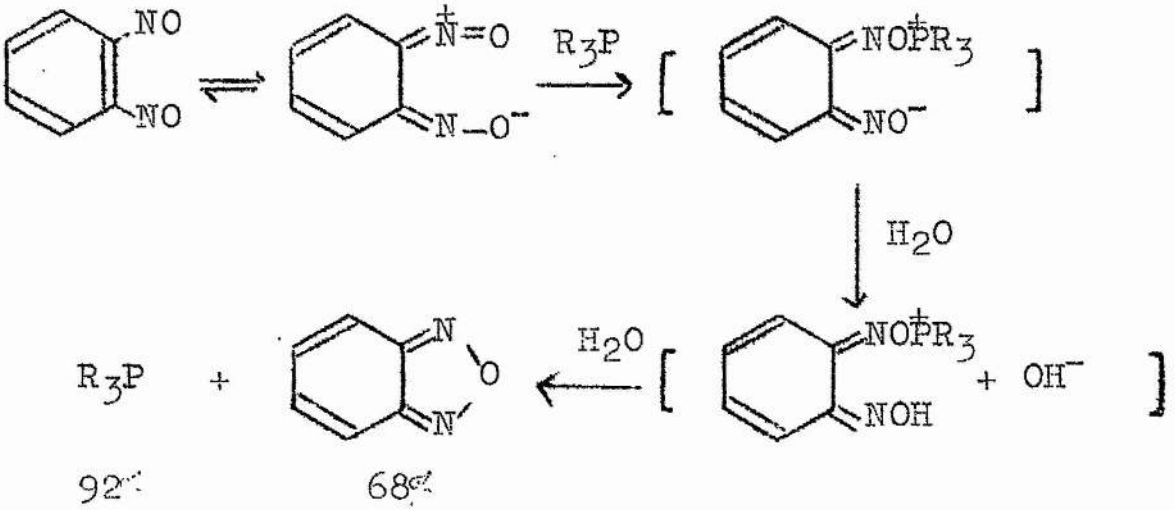


The experimental work so far does not allow any clear distinction to be made between these three suggested reaction mechanisms.

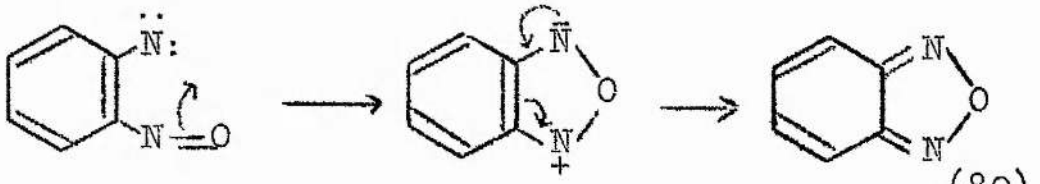
Thus the reactions of the nitrene intermediate have been studied in a variety of reactions outside the field of organophosphorus chemistry, and the similarity of its behaviour to that of the carbene intermediate has been noted. The application of the nitrene hypothesis to the mechanism of the deoxygenation of aromatic nitroso- and nitro-compounds by tervalent phosphorus reagents remains to be discussed.

(d) The mechanism of the reaction with aromatic nitroso-compounds. Although the mechanism of this reaction, and of that with aromatic nitro-compounds, will be discusseed further in the light of experimental work described in a later chapter, a summary of earlier work may be given at this point.

Prior to the first suggestion of nitrene participation in tervalent phosphorus deoxygenations,[72] Boyer and Ellzey[70] reported the deoxygenation of o-dinitrosobenzene to benzofurazan, and suggested a mechanism dependent upon the presence of water in the ethanol solvent. This was apparently confirmed when, with anhydrous petroleum ether as solvent, no benzofurazan was isolated:

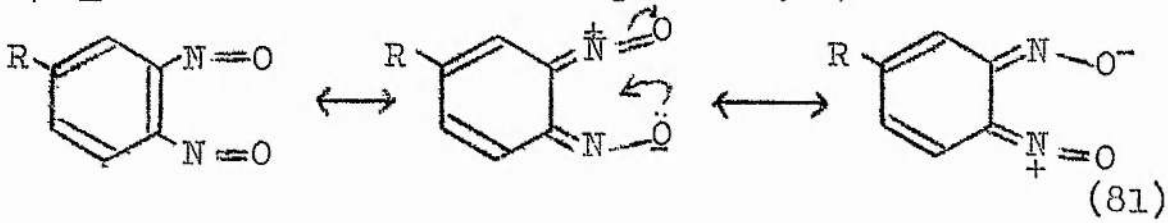


It was, however, suggested later[72] that a nitrene intermediate had been involved (80).



(80)

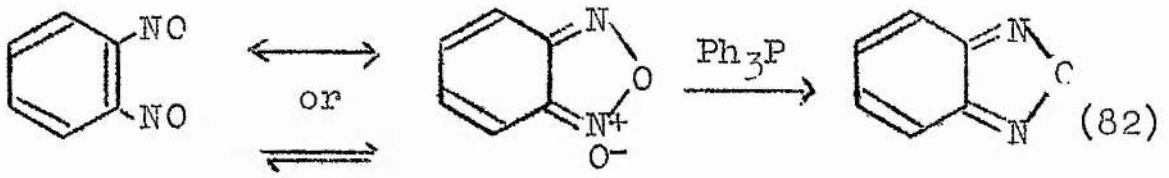
A third possibility might arise from the suggestion of Boyer et al.[136] that benzofuroxans may be considered as 1,2-o-dinitroso-aromatic compounds (81):



(81)

This has been discussed further by Katritzky,[137] and Bailey and Case.[138] Should this be so, and if, in turn, o-dinitrosobenzenes react as benzofuroxans, then the reaction might, in this case, be directly via

benzofuroxan to benzofurazan. (82)

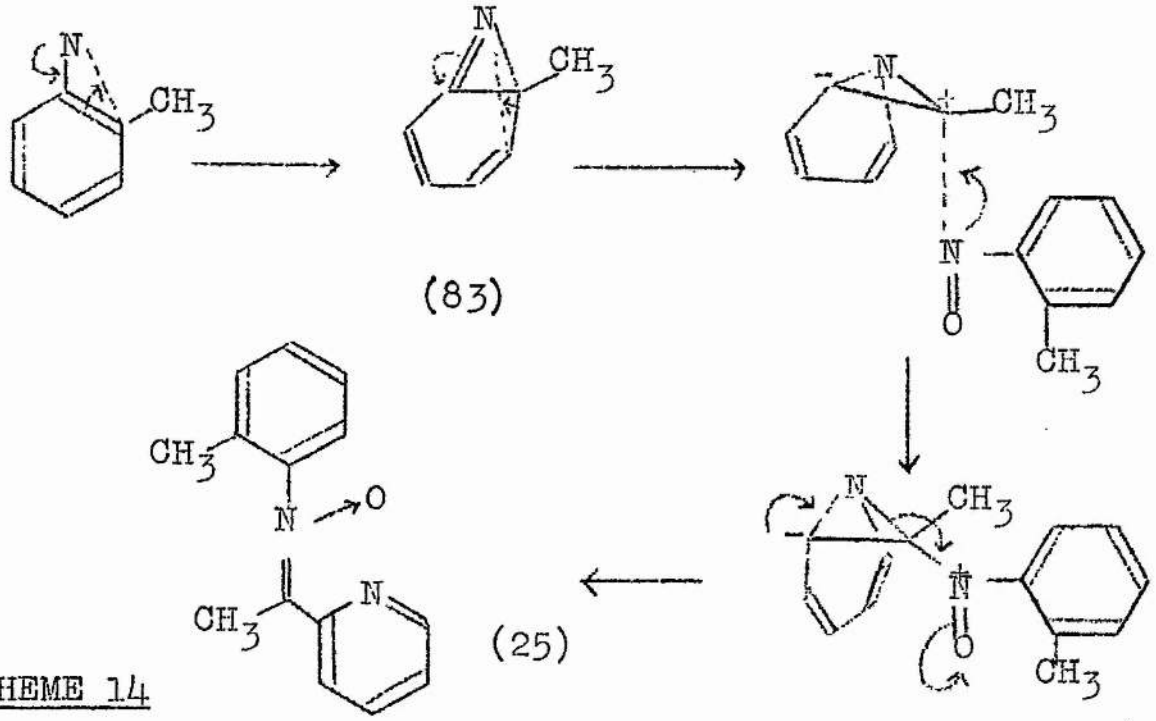


(82)

This last reaction has been reported by Cadogan et al.[74] in the deoxygenation of o-nitronitrosobenzene to benzofurazan by triethyl phosphite.

Bunyan and Cadogan,[72] in their paper on the deoxygenation of C-nitroso-compounds by triethyl phosphite, attributed the formation of azoxy-compounds from o-ethylnitrosobenzene and p-dimethylaminonitrosobenzene to attack on unchanged nitroso-compound by a nitrene intermediate. In agreement with this hypothesis, an increase in the relative amount of triethyl phosphite used in the latter case caused a decrease in the amount of azoxy-compound, and an increase in the proportion of N-p-dimethylaminophenylphosphorimidate. This latter product could obviously arise by interaction of the nitrene with triethyl phosphite in a reaction similar to the formation of methylenephosphoranes from triphenylphosphine and carbenes.[139]

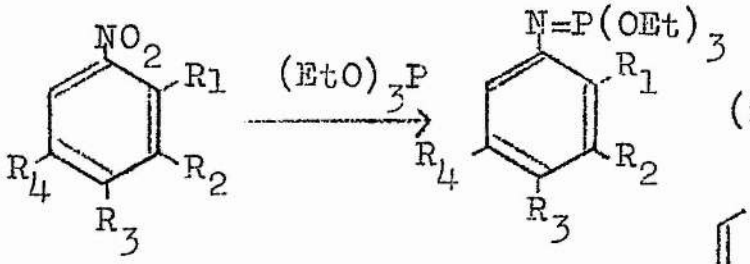
Sundberg,[73] in his re-investigation of the deoxygenation of a number of o-alkylnitrosobenzenes, isolated a number of amines (from H-abstraction) and



(83)

(25)

SCHEME 14

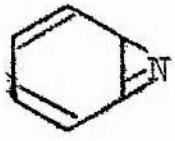


(27) + (26)

R_1	R_2	R_3	R_4	% (26)	% (27)
H	H	H	H	0	1
H	H	CH_3	H	0	3
CH_3	H	H	H	37	13
CH_3	CH_3	H	H	18	22
CH_3	H	CH_3	H	10	51
CH_3	H	H	CH_3	4	14
H	H	CH_3O	H	0	34

SCHEME 15

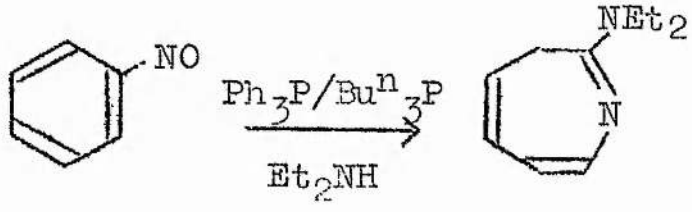
cyclised products (from C-H insertion) consistent with the intermediacy of a nitrene. Unfortunately, as in many such reactions, the major "product" was an intractable, brittle glass which defied distillation. The possibility that the skeletal rearrangement products (25,26) had arisen from the nitrene, through the 7-azabicyclo[4,10]heptatriene intermediate (83) proposed earlier by Huisgen[126] was discussed (Scheme 14).



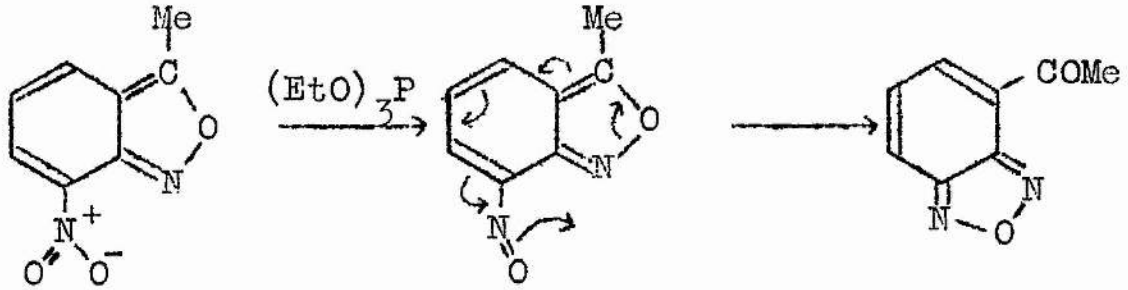
(83)

However, in the light of later results, from the photolysis of o-alkylnitroaromatics in triethyl phosphite,[85] (Scheme 15), the suggested mechanism has been withdrawn. Both schemes will be discussed later.

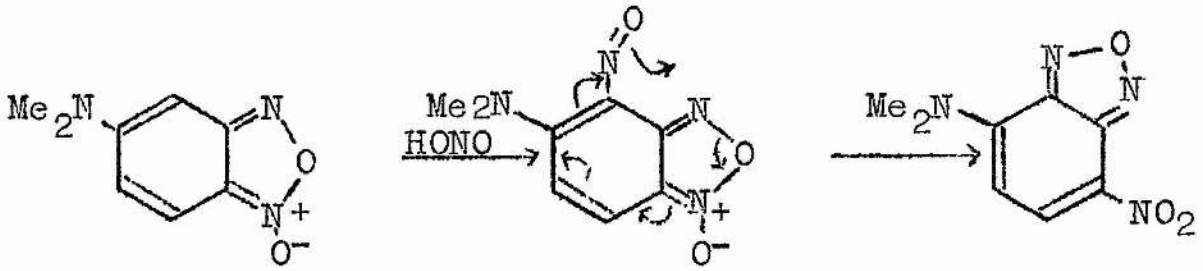
Further evidence for nitrene participation in these reactions was provided by the report of Odum and Brenner[140] that 2-diethylamino-3H-azepine (84) had been prepared by the reaction of nitrosobenzene and triphenyl- or tributylphosphine in diethylamine. This was of course, directly parallel to their earlier work[119] on the photolysis of phenyl azide in diethylamine. (72)



62% (84)

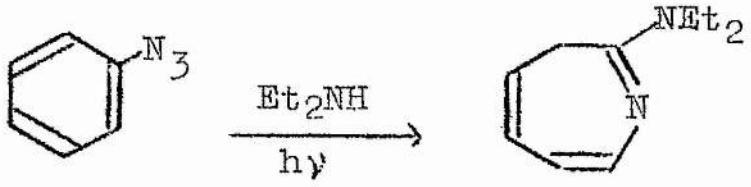


(85) (86)



(87)

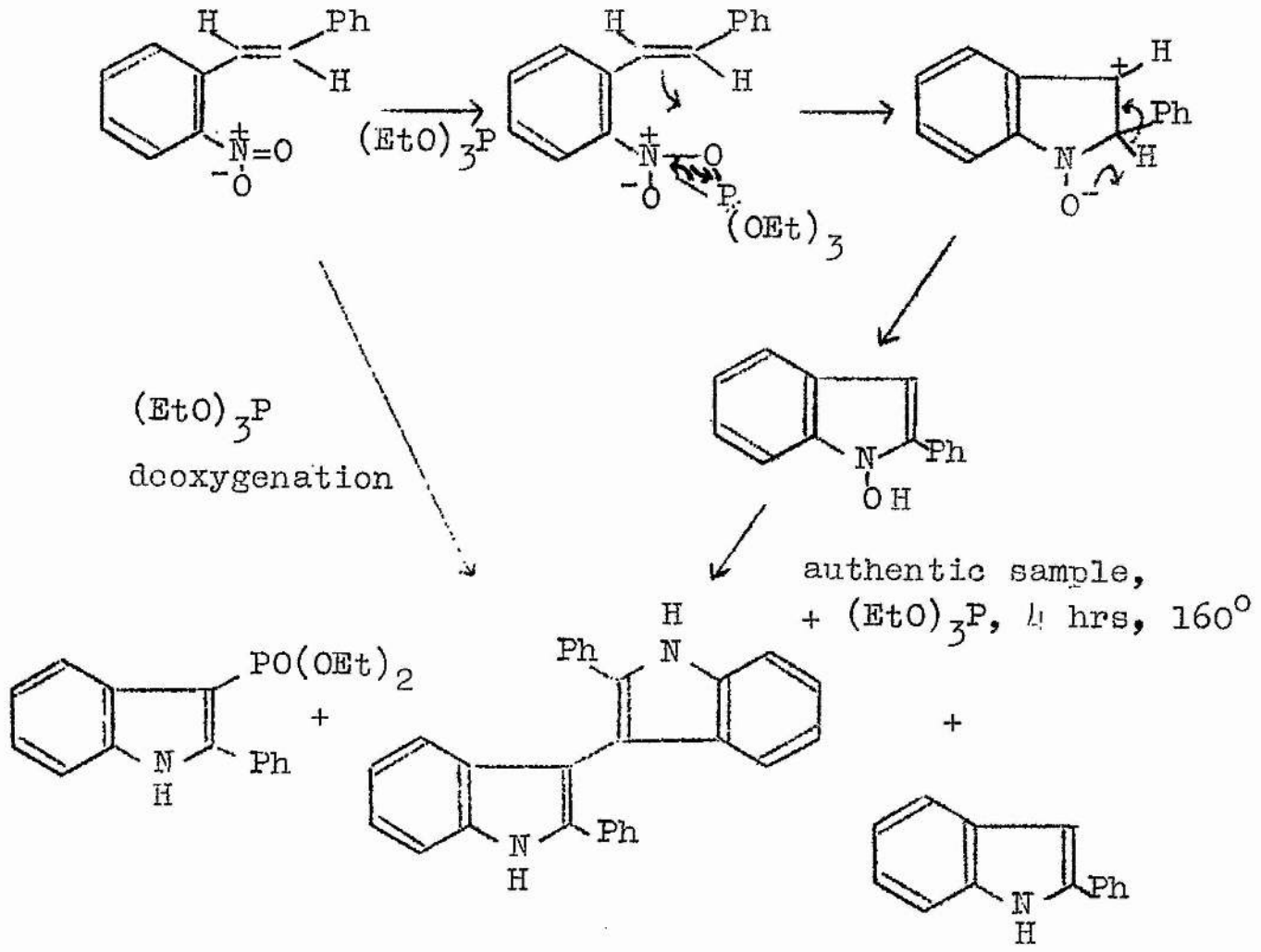
SCHEME 16



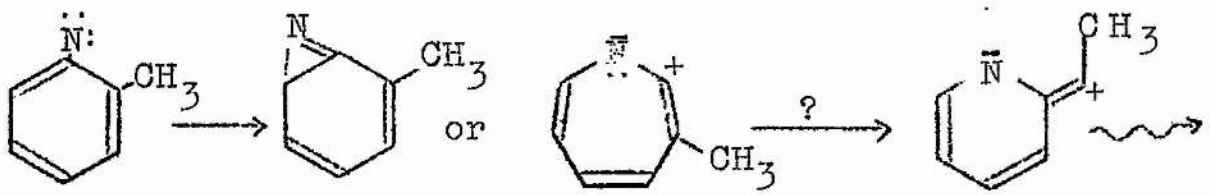
(72)

Weingarten[141,142] in one of the few comparative studies of the chemistry of tervalent phosphorus and arsenic reagents, reported that both trisdimethylaminophosphine and trisdimethylaminoarsine gave azoxybenzene from their reactions with nitrosobenzene. The main divergence in their chemistry was due to the formation of the stable trisdimethylaminophosphine oxide, which has no known arsenic analogue.

(e) The mechanism of the reaction with aromatic nitro-compounds. The extension of the deoxygenation reaction to aromatic nitro-compounds[74,79,143] again gave results broadly consistent with the intermediacy of a nitrene. It was suggested that the reaction followed an initial nucleophilic attack on both nitro- and nitroso-oxygen, possibly with intermediate reduction of the nitro-compound to the more reactive nitroso-compound. The only evidence for this intermediacy of the nitroso-group came in a recent report[144] of the isolation of 4-acetylbenzofurazan (86) from the reduction of 3-methyl-7-nitro-anthranil (85). In view of earlier work[145] on the reactions of 4-nitrosobenzofuroxan (87), a nitroso-intermediate is at least


(EtO)3P
deoxygenation
authentic sample,
+ (EtO)3P, 4 hrs, 160°
PO(OEt)2
1 - 10%
7 - 20%
79%

SCHEME 17


or
?

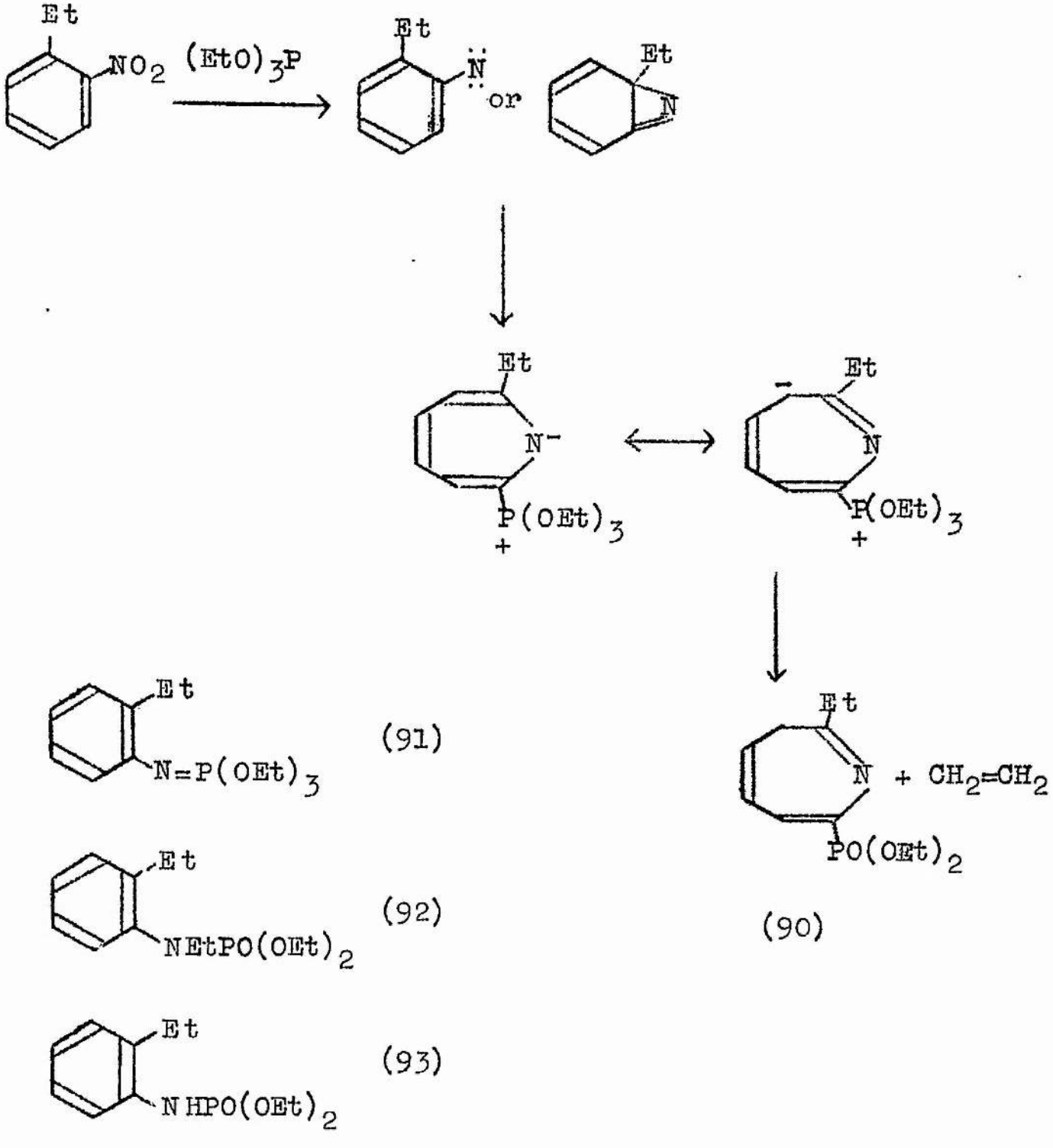
possible in this particular reaction (Scheme 16).

As an alternative to this nitro-nitroso-nitrene system, Sundberg[86] has postulated the intermediacy of 1-hydroxyindoles (88) in the indole syntheses described earlier.[86-88] 1-Ethoxyindoles were isolated as by-products, presumably as a result of alkylation of the 1-hydroxyindoles by triethyl phosphate.

In one particular case, 1-hydroxy-2-phenylindole (15%) was isolated after one hour from the reaction mixture. Treatment of an authentic sample of 1-hydroxy-2-phenylindole with an excess of triethyl phosphite resulted in the same product distribution as in the original reaction (Scheme 17).

In contrast to this, o-ethylnitrobenzene, the fully-saturated analogue of these olefins, gave mainly triethyl N-o-ethylphenylphosphorimidate under similar conditions.

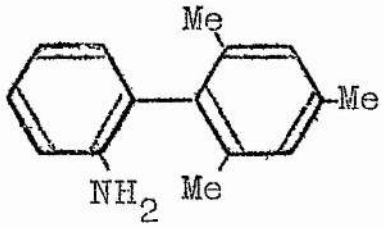
Further investigations of the reactions of o-alkyl-nitrobenzenes with triethyl phosphite under thermal[73] and photolytic[85] conditions suggested that the nitrene-azirine-azepine rearrangement (89) might be taking place. The formation of the final skeletal rearrangemnt product was recorded in the photolytic reaction only. A more detailed mechanism is still awaited.


Et
NO2
(EtO)3P
Et
N
or
Et
N
Et
N-
P(OEt)3
+
Et
N
P(OEt)3
+
Et
N
+ CH2=CH2
PO(OEt)2
(90)
Et
N=P(OEt)3
(91)
Et
NEtPO(OEt)2
(92)
Et
NHPO(OEt)2
(93)

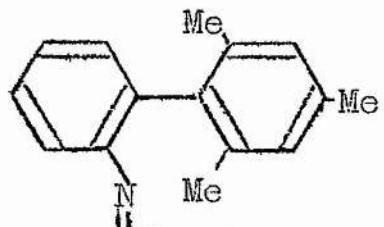
SCHEME 18

A recent communication from Cadogan et al.[146] reported the isolation of diethyl 2-ethyl-3H-azepin-7-ylphosphonate (90,12%) as an additional product from the reaction of triethyl phosphite with o-ethylnitrobenzene. The other products of the reaction were triethyl N-o-ethylphenylphosphorimidate (91), diethyl N-ethyl-N-o-ethylphenylphosphoramidate (92), and N-o-ethylphenylphosphoramidate (93) (Scheme 18). In the absence of diethylamine, triethyl phosphite itself might act as the nucleophile to give a phosphonium intermediate, from which ethylene (50% based on azepine) was then eliminated to give the azepine.

Further evidence for nitrene participation was provided by the reaction of an excess of triethyl phosphite with 2'-nitro-2,4,6-trimethylbiphenyl[147] to give 2'-amino-2,4,6-trimethylbiphenyl (94,13%), presumably via hydrogen abstraction, and triethyl N-(2',4',6'-trimethylbiphenyl-2-yl)phosphorimidate (95,15%).

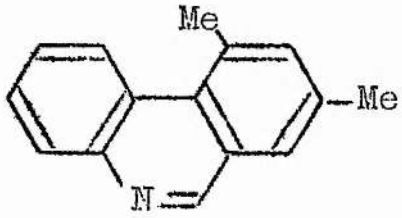


(94)

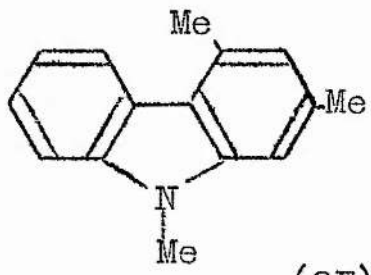


(95)

The amine (94) had been obtained, amongst other products, (96,97), by Smolinsky[148] in an examination of the thermal decomposition of 2'-azido-2,4,6-trimethylbiphenyl. When the reaction was carried out in the presence of isopropylbenzene, hydrogen abstraction led to the formation of bi-α-cumyl (11% isolated). Insertion products (96,97) were, however, not detected.

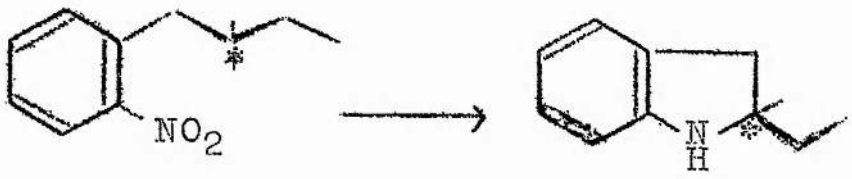


(96)



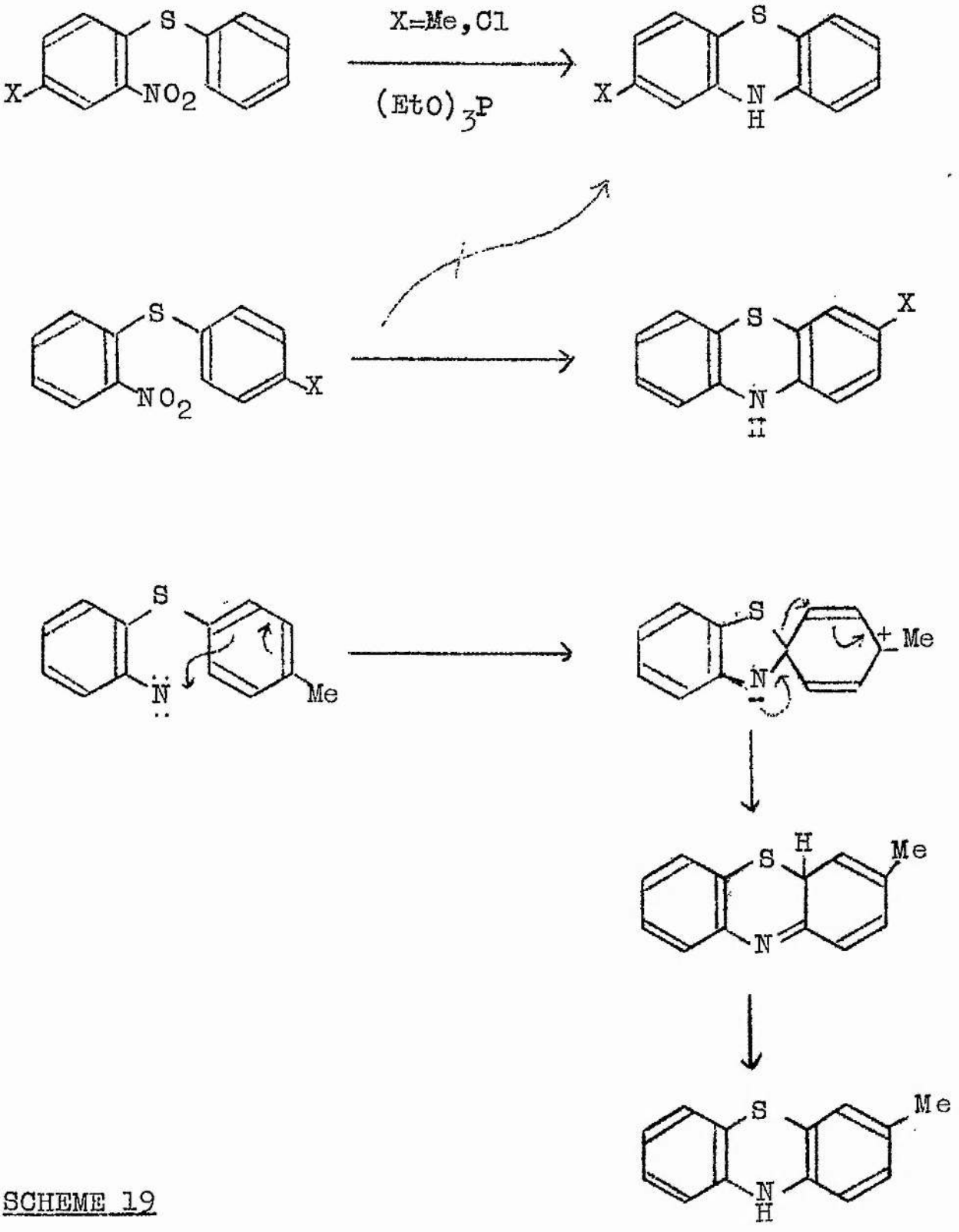
(97)

Smolinsky also studied the reaction of (+)-(S)-2-nitro-1-(2-methylbutyl)benzene with triethyl phosphite,[149] from which he obtained a partially-active (50%) indoline (98, 25%).

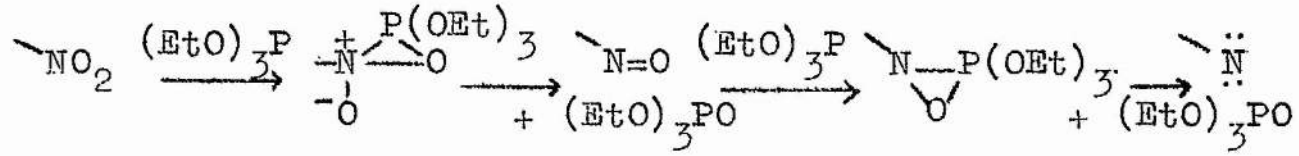


(98)

This was compared with a 60% yield of 65% active indoline from the decomposition of the corresponding azide (Scheme 9). It was suggested that the deoxygenation of the nitro-group was a two stage process via nitroso- to nitrene:



SCHEME 19



Finally, a detailed investigation of the synthesis of phenothiazine from 2-nitrophenyl phenyl sulphide[89] has revealed a new molecular rearrangement.[150] Thus, while 4-methyl-2-nitrophenyl phenyl sulphide gave 2-methylphenothiazine (36%) and N-ethyl-2-methylphenothiazine, the isomeric 4-methylphenyl 2-nitrophenyl sulphide gave 3-methylphenothiazine and its N-ethyl derivative. When the reaction was carried out in cumene, 4-chloro-2-nitrophenyl phenyl sulphide gave 2-chlorophenothiazine (55%) while 4-chlorophenyl 2-nitrophenyl sulphide gave 3- (63%) rather than 2-chlorophenothiazine (Scheme 19). Once again, the participation of a nitrene intermediate is postulated. The six-membered ring may be formed by rearrangement of a five-membered spiro-intermediate formed, in turn, by electrophilic attack at the electron-rich 1'-position.

(f) Other deoxygenation reactions of tervalent phosphorus reagents. The deoxygenation of some pyridine-N-oxides has been studied briefly, but generally without the isolation of any product other than the oxidised phosphorus moiety. 4-Nitropyridine-N-oxide, when heated with triphenylphosphine in the

absence of any solvent, gave brown nitrous fumes and a black tar, from which only triphenylphosphine oxide was isolated.[151] When the reaction was carried out in boiling chloroform, the conditions were too mild for a reaction to take place.

A free-radical process was suggested for the reaction of triethyl phosphite with 4-nitropyridine-N-oxide.[152,153] The reaction, catalysed by both peroxides and oxygen, had a rate of reaction which varied with the state of the solvent and was generally non-reproducible.

Nitrile oxides,[154] β-nitrostyrene[155] and 1-nitrophenylethane,[149] and various isocyanates[156] have been reduced to the corresponding nitriles by tervalent phosphorus reagents:

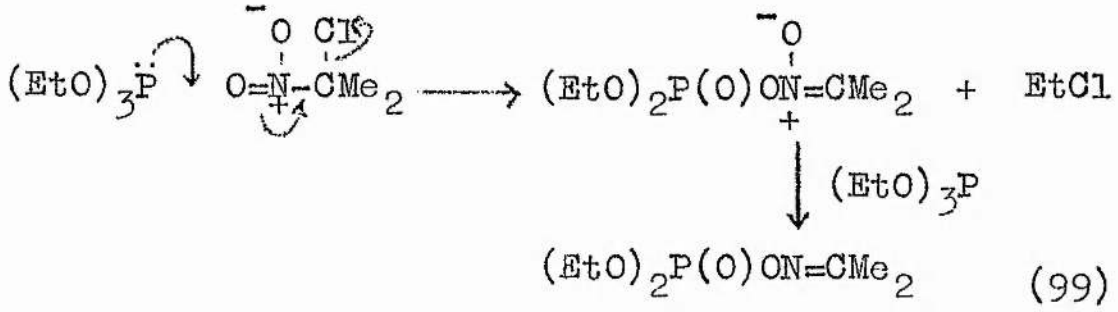
$$RC{\equiv}NO \xrightarrow{Ph_3P} RC{\equiv}N + Ph_3PO$$

$$PhCH{=}CHNO_2 \xrightarrow{Ph_3P} PhCH_2CN \xleftarrow{(EtO)_3P} PhCH_2CH_2NO_2$$

$$ROCN \xrightarrow{(EtO)_3P} RCN + RNC + (RO)_3PO + (RO)_2POCN$$

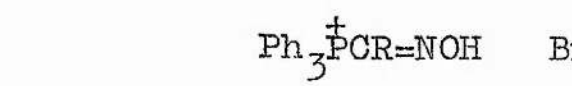
Simple aliphatic nitro-compounds show few reactions with tervalent phosphorus reagents. Under mild conditions, no reaction at all occurs.[157] Allen[158] showed that 2-chloro-2-nitropropane reacted with triethyl phosphite

to give diethyl isopropylideneaminophosphate (99), triethyl phosphate and ethyl chloride.



(99)

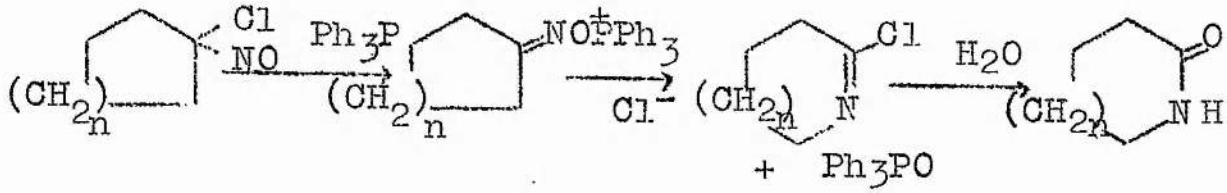
Trippett[159,160] investigated the reaction of various 1-halo-1-nitroalkanes with triphenylphosphine. The phosphonium salt intermediate was shown to be an α-hydroxyiminoalkylphosphonium bromide (100)[160] rather than the α-nitroalkylphosphonium bromide, as suggested earlier.[159]



(100)

Similar investigations have been carried out by Speziale and Smith.[161]

Ohno has reported the first succesful Beckmann rearrangement of gem-halonitrosocycloalkanes.[162]



The corresponding nitro-compounds are reported to behave in a similar fashion.[163]

4. Summary

At the time that this investigation commenced, the reactions of tervalent phosphorus reagents with simple bifunctional aromatic nitro-compounds, such as o-dinitrobenzene, and with alkylnitrobenzenes, such as o-ethylnitrobenzene, had received little attention.

Earlier reports had shown that o-dinitrobenzene, with triphenylphosphine, gave a 1:1 adduct,[164] whereas both o-dinitroso-[70] and o-nitronitroso-benzene,[74] with triethyl phosphite, gave benzofurazan. The reaction of triethyl phosphite with o-dinitrobenzene gave a solid product, isolated by chromatography, which could not be characterised further.[165]

While the reaction of tervalent phosphorus reagents with o-substituted nitrobenzenes, with phenyl or other unsaturated groups adjacent to the nitro-group, had been fully discussed,[74] the corresponding reactions with the saturated alkyl analogues had not.

It was decided therefore, that these reactions should be investigated in turn, to clarify the mechanism of the reactions, and to extend the scope of the reaction for synthesis.

EXPERIMENTAL

1. (a) Instrumentation and Analysis.

Infra-red (i.r.) spectra were recorded on a variety of Perkin-Elmer Infra-red Spectrophotometers, (Models 137, 237, 257, and 621). Solids were examined as Nujol mulls or as thin-film melts, and liquids as thin films. Ultra-violet (u.v.) spectra were recorded on a Unicam S.P. 800 Spectrophotometer.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin-Elmer Model R.10. Nuclear Magnetic Resonance Spectrometer, operating at 60 Mc./sec., with a probe temperature of 34°. Chemical shifts were recorded as tau (τ) values, employing tetramethylsilane (T.M.S.) as an internal reference (τ=10.0).

Quantitative gas-liquid chromatography (g.l.c.) was carried out on a Griffin D6 Gas-Density Balance Chromatograph, using 2m., $\frac{1}{4}$" O.D. columns, and nitrogen as the carrier gas. Quantitative and analytical g.l.c. studies were also performed on Perkin-Elmer F11 , and Varian "Aerograph" 1520 B instruments. Both used 2m., $\frac{1}{8}$" O.D. columns with nitrogen as the carrier gas, and were fitted with temperature-programmed ovens and flame-ionisation detectors. Where necessary, a Varian Salt-tip (Caesium Bromide) Phosphorus Detector was used with the Model 1520 B flame-ionisation unit. Alternatively,

the Model 1520 B chromatograph could be used with a Gow-Mac 625 gas-density balance, requiring $\frac{1}{4}$" O.D. columns. This could in turn be used in conjunction with a collection unit, supplied by Research and Industrial Instruments Ltd., for the trapping of individual g.l.c. separated reaction products in silver chloride micro-cells for i.r. analysis.

Large-scale g.l.c. separations were carried out with a Pye 105 Automatic Preparative Chromatograph, using $\frac{1}{4}$" O.D. glass columns.

The g.l.c. stationary phases used were neopentyl glycol succinate (N.P.G.S.), fluorosilicone oil FS-1265 (Q.F.-1), polyethylene glycol adipate (P.E.G.A.) and Apiezon 'L' (A.P.L.), absorbed on celite.

The use of the gas-density balance in quantitative work depends on the relationship which exists between the integral response of the detector, the peak area in this case, and the molecular weight of the compound passing through it.[166] The relationship is stated as follows:

$$n = \frac{kA}{M-m}$$

where n = number of moles injected,

m = molecular weight of the carrier gas,

k = constant dependent on the characteristics of the instrument,

A = peak area,

M = molecular weight of the compound.

Therefore, for a mixture of compounds, and using nitrogen as the carrier gas :-

$$\frac{n_1}{n_2} = \frac{A_1(M_2-28)}{A_2(M_1-28)}$$

If one of the compounds is an unreactive internal standard, present in measured amounts, then the number of moles of the other compound present in the reaction mixture may be calculated at any time by comparison of the areas of the g.l.c. peaks due to the two compounds.

Quantitative estimation by means of a chromatograph fitted with a flame-ionisation detector requires prior calibration of the instrument with authentic samples of each component to be measured, against some internal standard.

Melting points were determined using a Kofler hot-stage microscope, and are corrected. Refractive indices were measured at a specified temperature in the range 20-25° on a Hilger Abbe Refractometer. Molecular weights were determined on a Mechrolab Vapor Pressure

Osmometer 301 A. Microanalyses were carried out by Dr. Alfred Bernhardt, Muhlheim, Germany; by Dr. G. Weiler and Dr. F.B. Strauss at Oxford, and by Mr. J. Bews on a Perkin-Elmer Model 240 Elemental Analyser in this Department.

(b) Preparation of Starting Materials and Authentic Samples.

Benzene, ether, and light petroleum (b.p. 40-60°) were redistilled and stored over sodium wire. Acetonitrile and dimethylformamide were dried over phosphorus pentoxide and calcium hydride, respectively, before redistillation.

Nitrobenzene, o-, m-, and p-nitrotoluene, o and p-ethylnitrobenzene, o-, m-, and p-dinitrobenzene, o-, m-, and p-nitroanisole, o-chloronitrobenzene, o-nitrobenzonitrile, and chloro-2,4-dinitrobenzene were purified by distillation or recrystallisation. 1,2,4-Trinitrobenzene, m.p. 56°, was prepared in 89% yield by the oxidation of 2,4-dinitroaniline with peroxytrifluoroacetic acid.[167]

o-Methyl- and o-ethylnitrosobenzene, m.p. 71° and 61° respectively, were prepared in 30% yield by reduction of the corresponding nitro-compounds with zinc dust in neutral solution.[168]

2-Nitropyridine, m.p. 71°, was prepared in 76% yield

by the oxidation of 2-aminopyridine with fuming sulphuric acid and hydrogen peroxide (30%).[169] 2-Nitropyridine-N-oxide, m.p. 85°, (lit.[170,171], 85-86°), was prepared by the oxidation of 2-acetamidopyridine-N-oxide with Caro's acid;[171] attempts to synthesise this nitro-compound by Brown's method,[170] [oxidation of 2-amino-pyridine-N-oxide with fuming (30%) sulphuric acid and hydrogen peroxide (30%)], proved unsuccessful. 4-Nitro-pyridine-N-oxide was commercially available.

Aniline, o-, m-, and p-toluidine, o-, m-, and p-anisidine and o- and p-ethylaniline were purified prior to use by distillation from a trace of zinc dust, or by recrystallisation. N,2-diethylaniline, b.p. 94°/12 mm., was prepared from o-ethylaniline and ethyl iodide.[172]

2,2'-Dimethyl- and -diethylazoxybenzene were prepared by oxidation of the corresponding azo-compounds by peracetic acid.[173] 2,2'-Diethylazoxybenzene had m.p. 18-20°, (lit.[173], 12-13°), with i.r. spectrum identical to that described. 2'2'-Dimethylazoxybenzene had m.p. 57-58°, (lit.[174], 59°).

Trimethyl, triethyl, and tri-isopropyl phosphite were distilled at reduced pressure from sodium wire. Diethyl methylphosphonite of purity better than 95%, kindly supplied by the Chemical Defence Experimental Establishment,

Porton, was used without further purification. Triphenylphosphine, recrystallised from ether, had m.p. 79-80°. Tri-n-butylphosphine was used without distillation. Trisdiethylaminophosphine, b.p. 85-90°/12mm., was prepared in 55% yield from phosphorus trichloride and diethylamine.[175] Ethyl diphenylphosphinite, b.p. 178°/14mm., was prepared in 85% yield from chlorodiphenylphosphine and absolute ethanol in the presence of triethylamine.[176]

All reactions involving tervalent phosphorus reagents were carried out in an atmosphere of dry, oxygen-free, nitrogen.

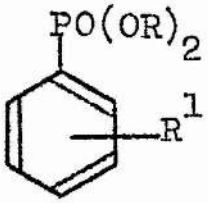
Trisdiethylaminophosphine oxide, b.p. 91°/0.01mm., was prepared from phosphorus oxychloride and diethylamine.[177] Dimethyl methylphosphonate, b.p. 72°/14mm., was prepared by heating trimethyl phosphite under reflux with a trace of methyl iodide.[178]

Ethyl diphenylphosphinate. An excess of hydrogen peroxide (100 vol.) (10 ml.) was added, with care, to a solution of ethyl diphenylphosphinite (1.05g.) in benzene (5ml.) at 20°. When the exothermic reaction had subsided, the solvent and the excess of hydrogen peroxide were removed under reduced pressure, and the remaining colourless liquid was distilled to give ethyl diphenyl-

phosphinate (1.08g., 96%), b.p. 159°/0.03mm. (Found: C, 68.1; H, 6.0; P, 12.7. $C_{14}H_{15}PO_2$ requires C, 68.3; H, 6.1; P, 12.6%). G.L.C. confirmed that this was a single compound. The i.r. spectrum [ν_{max}: (P=O), 1230; (P-O-Et), 960, 1020-1050, 1165 cm^{-1}.], and n.m.r. spectrum (carbon tetrachloride) [$P\cdot OCH_2\underline{CH_3}$, triplet, 3H, τ = 8.70; $P\cdot O\underline{CH_2}\cdot CH_3$, quintet, 2H, τ=6.00; aromatic, multiplet, 10H, τ = 2.05-2.80] confirmed this structure. All published data for this compound[179-181] refer to a preparation by Michaelis,[182] in which he assigned this structure to a solid m.p. 165°. Quin and Anderson[176] reported a solid m.p. 167-169° as a by-product in the preparation of ethyl diphenylphosphinite, described earlier: the i.r. spectrum was identical with that of tetraphenyldiphosphine dioxide. It may be, therefore, that the published data refer to this compound, rather than to ethyl diphenylphosphinate. Our assignment, however, appears to be correct.

Dialkyl arylphosphonates. The synthetic method recently described by Obrycki and Griffin[183] was used for the preparation of a number of dialkyl arylphosphonates: the following was typical. A solution of p-iodotoluene (5 g.) in an excess of triethyl phosphite (75 ml.) was irradiated for 20 hrs. at 0° by a "Hanovia",

TABLE 1



dialkyl arylphosphonates.

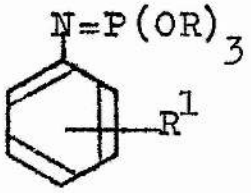
R^1	R	b.p. °/0.1 mm.	lit.[183] b.p. °/ mm.
o-Me	Me	85-86	96-97/0.25
m-Me	Me	90-92	106-107/0.45
p-Me	Me	90-94	93-94/0.05
o-OMe	Me	108-110	110-112/0.1
m-OMe	Me	110-112	116-117/0.1
p-OMe	Me	110-112	113-114/0.1
o-Me	Et	83-85	105-107/0.3
m-Me	Et	85-86	104-105/0.4
p-Me	Et	90-95	148-149/4.0
p-Et	Et	92-94	110-112/0.3
o-OMe	Et	120-123	120-121/2.0

100 W., medium pressure, water-cooled u.v. lamp. The colourless reaction mixture was distilled at reduced pressure, the final fraction yielding diethyl p-tolylphosphonate (4.7 g., 76%), b.p. 90-95°/0.1 mm., (lit.[183] 148-9°/4.0 mm.). The i.r. and n.m.r. spectra agreed with that reported. The phosphonates described in TABLE 1 were prepared in a like manner.* In addition, diethyl m-methoxyphenylphosphonate, b.p. 120-122°/0.10 mm. (Found: C, 54.3; H, 7.0. $C_{11}H_{17}O_4P$ requires C, 54.1; H, 7.0%.), and diethyl p-methoxyphenylphosphonate,[184,185] b.p. 127-130°/0.10 mm. (Found: C, 53.95; H, 7.2. Calc. for $C_{11}H_{17}O_4P$: C, 54.1; H, 7.0%) were prepared. The i.r. and n.m.r. spectra of these compounds, and of those in TABLES 2, 3 and 4 are given later.

This preparation is unsatisfactory with iodonitrobenzenes.[183] Diethyl p-nitrophenylphosphonate was, therefore, prepared by an alternative method. p-Nitrophenylphosphonic acid, m.p. 195-6° (lit.[186] 197-8°) was prepared by the method of Doak and Freedman[187] from p-nitrobenzenediazonium fluoroborate and phosphorus trichloride in ethyl acetate. The acid was esterified

*I am most grateful to Mr. M. Grunbaum and Mr. G. Clement for assistance in the preparation of these series of authentic samples.

TABLE 2



trialkyl N-arylphosphorimidates

R^1	R	b.p. °/ mm.	Mol. formula	Found % C	Found % H	Required % C	Required % H
o-Me	Me	93-97/0.05	$C_{10}H_{16}NO_3P$	52.4	7.3	52.4	7.0
m-Me	Me	92-95/0.04[a]	"	52.4	7.2	"	"
p-Me	Me	99-102/0.05[b]	"	52.35	7.2	"	"
o-OMe	Me	110-113/0.02	$C_{10}H_{16}NO_4P$	48.7	6.6	49.0	6.5
m-OMe	Me	108-112/0.02	"	48.6	6.6	"	"
p-OMe	Me	103-107/0.01[c]	"	48.6	6.7	"	"
m-Me	Et	99-100/0.04	$C_{13}H_{22}NO_3P$	57.4	8.4	57.6	8.1
p-Me	Et	98-99/0.05	"	57.3	8.0	"	"
o-OMe	Et	108-111/0.02	$C_{13}H_{22}NO_4P$	54.2	7.9	54.4	7.65
m-OMe	Et	103-106/0.02	"	54.1	7.8	"	"
p-OMe	Et	109-116/0.02	"	54.4	7.9	"	"
o-Et	Et	93-97/0.03[d]	$C_{14}H_{24}NO_3P$	59.2	8.3	59.0	8.4

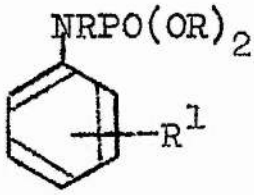
a lit.[190] 55-56°/0.001 mm.

b lit.[190] b.p. not given.

c lit.[190] 55-56°/0.001 mm.

d lit.[200] 90-100°/0.05 mm.

TABLE 3



dialkyl N-alkyl-N-arylphosphoramidates

R^1	R	b.p. °/ mm.	Mol. Formula	Found % C	Found % H	Required % C	Required % H
o-Me	Me	96-97/0.02	$C_{10}H_{16}NO_3P$	52.1	7.2	52.4	7.0
m-Me	Me	99-100/0.03[e]	"	52.2	7.3	"	"
p-Me	Me	90-93/0.03[f]	"	52.3	7.3	"	"
o-OMe	Me	104-106/0.02	$C_{10}H_{16}NO_4P$	48.6	6.8	49.0	6.5
m-OMe	Me	104-107/0.07	"	48.8	6.8	"	"
p-OMe	Me	108-109/0.03[g]	"	48.7	6.6	"	"
m-Me	Et	92-96/0.01	$C_{13}H_{22}NO_3P$	57.25	8.4	57.6	8.1
p-Me	Et	90-93/0.03	"	57.2	8.3	"	"
o-OMe	Et	101-102/0.01	$C_{13}H_{22}NO_4P$	54.3	8.0	54.4	7.65
m-OMe	Et	108-109/0.01	"	54.1	7.9	"	"
p-OMe	Et	110-113/0.03	"	54.2	7.9	"	"

e lit.[190] 93-94°/0.04 mm.

f lit.[190] 100-101°/0.1 mm.

g. lit.[190] 110-112°/0.04 mm.

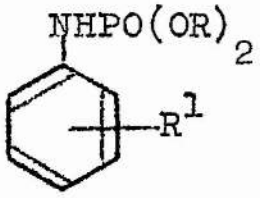
by reaction with absolute ethanol in the presence of N,N'-dicyclohexylcarbodi-imide;[197] the diethyl ester had b.p. 110-112°/0.1 mm. (lit.[188] 139-144°/0.3 mm.).

Trialkyl N-arylphosphorimidates. A series of trialkyl N-arylphosphorimidates were prepared from triethyl or trimethyl phosphite and the required aryl azide by the method of Kabachnik and Gilyarov.[189] Satisfactory i.r. and n.m.r. spectra were obtained in each case. The phosphorimidates described in TABLE 2 were prepared by this method.

Dialkyl N-alkyl-N-arylphosphoramidates. These compounds were obtained as yellow oils by heating the corresponding trialkyl N-arylphosphorimidate under reflux with the required alkyl iodide.[189,190] The i.r. and n.m.r. spectra were as expected and are described later. The phosphoramidates described in TABLE 3 were prepared by this method. Authentic samples of diethyl N-ethyl-N-o-ethylphenylphosphoramidate (R^1=o-Et, R=Et), b.p. 92-94°/0.03 mm., and diethyl N-ethyl-N-o-tolylphosphoramidate, (R^1=o-Me, R=Et), b.p. 120-130°/0.03 mm., were also available.[200]

Dialkyl N-arylphosphoramidates. Trialkyl N-arylphosphorimidates were hydrolysed to the corresponding phosphoramidates, over a period of three days, by

TABLE 4



dialkyl N-arylphosphoramidates

R^1	R	m.p.°	Mol. formula	Found % C	Found % H	Required % C	Required % H
o-Me	Me	110	$C_9H_{14}NO_3P$	50.5	6.6	50.3	6.5
m-Me	Me	97	"	50.4	6.7	"	"
p-Me	Me	108-109	"	50.4	6.7	"	"
o-OMe	Me	112-113	$C_9H_{14}NO_4P$	46.45	6.1	46.8	6.1
m-OMe	Me	108	"	47.0	6.0	"	"
p-OMe	Me	109-110	"	47.1	6.0	"	"
m-Me	Et	98	$C_{11}H_{18}NO_3P$	54.8	7.5	54.4	7.4
p-Me	Et	95	"	54.35	7.6	"	"
o-OMe	Et	99-102	$C_{11}H_{18}NO_4P$	51.2	6.9	51.0	6.95
m-OMe	Et	108-109	"	50.7	6.7	"	"
p-OMe	Et	113	"	50.9	6.9	"	"

adsorption on silica gel in benzene.[72] The resulting yellow crystalline solids were recrystallised from light petroleum to give pure samples of the desired compounds. An alternative method, the reaction of the phosphorimidates in hydrocarbon solution with dry hydrogen chloride gas,[189] was less successful, giving largely the aniline hydrochlorides. The phosphoramidates described in TABLE 4 were prepared by this method.

2. Reactions of o-Dinitrobenzene and Related Compounds with Tervalent Phosphorus Reagents.

In this series of experiments, authentic samples of the products were not generally available: identification was therefore by means of their chemical properties and by their i.r. and n.m.r. spectra. These spectra are described briefly in the text at the appropriate place. In cases where a discussion of the interpretation of the spectra is necessary, or where it is thought desirable to record the spectrum of a new compound, the i.r. and n.m.r. spectra are recorded in full in a later chapter.

Reaction of o-dinitrobenzene with triethyl phosphite. (a) Reactions without solvent, and in the presence of an excess of triethyl phosphite. o-Dinitrobenzene (7.80 g., 46 m. mole) and triethyl phosphite (30.08 g., 182 m. mole)

were heated under reflux, in an atmosphere of nitrogen. As the temperature of the reaction mixture reached 90-95°, a vigorous exothermic reaction took place, causing the excess of triethyl phosphite to boil (b.p. 160°), and the colour of the solution to change from pale yellow to very dark brown. After five minutes the vigorous reaction subsided, and the solution was maintained at 100° for two hours.

Distillation gave triethyl phosphite (13.5 g., 81 m. mole), b.p. 41°/14 mm., and triethyl phosphate (10.4 g., 5.7 m. mole), b.p. 80-86°/14 mm., 40-44°/ 0.02mm., identified by comparison of their i.r. spectra with those of authentic samples. Further distillation of the dark, viscous, residue gave a clear orange distillate, b.p. 128°/0.02 mm., which solidified on cooling. Recrystallisation from petroleum (b.p. 60-80°) gave fine colourless needles of <u>diethyl o-nitrophenyl-phosphonate</u>, (6.09 g., 23 m. mole, 50%), m.p. 55-56°. (Found: C, 46.25; H, 5.4; N, 5.6; P, 12.1 %. Mol. Wt. = 248-250. $C_{10}H_{14}NO_5P$ requires C, 46.4; H, 5.4; N, 5.4; P, 12.0 %. Mol. Wt. = 259). The i.r. spectrum showed ν_{max}:(P=O), 1247; (P-Ph), 1430; (P-O-C), 1020, 970, 960; (NO_2), 1530, 1367 cm^{-1}. The H^1 n.m.r. spectrum (carbon tetrachloride) showed P·O$CH_2\underline{CH_3}$, triplet, 6H, τ= 8.62; P·O$\underline{CH_2}CH_3$, quintet, 4H, τ= 5.81; aromatic, multiplet, 4H, τ= 2.25. The P^{31}

n.m.r. spectrum (ethanol) showed a complex band at δ = -10.5 p.p.m. relative to 85% phosphoric acid (external standard) suggesting that the phosphorus atom was bonded directly to the aromatic ring.

This experiment was repeated with the intention of trapping any volatile products of the reaction. The stream of nitrogen, which passed over the surface of the reaction mixture, was directed up the condenser and through a "Card-Ice"/ethanol cold trap. (In some experiments, liquid air was used as a coolant in place of this freezing mixture.) o-Dinitrobenzene (11.5 g., 69 m. mole) and triethyl phosphite (40.5 g., 244 m. mole) were heated together as before. During the course of the reaction, a colourless solid (at -60°) collected in the cold trap. This was purified by distillation into a second cold trap, and identified as ethyl nitrite, (1.3 g., 17 m. mole, 25%), b.p. 16°/760 mm., by comparison with an authentic sample.[191] The i.r. spectrum showed ν_{max}: (ONO), 1682, 1668; 1632, 1618 cm^{-1}. for a vapour-phase sample,[192] and the n.m.r. spectrum[193] (carbon tetrachloride) showed $-CH_2\underline{CH_3}$, triplet, 3H, τ = 8.60; $-\underline{CH_2}CH_3$, quartet, 2H, τ = 5.22. The mass spectrum was also in agreement with published results.[194]

This identity was confirmed chemically by the

in situ nitrosation of 1-indanone in the presence of acetic anhydride, under acidic conditions.[195] 2-Nitroso-1-indanone, m.p. 203-4°, formed as a colourless solid, showed no depression of melting point with an authentic sample, kindly provided by Mr. John Dingwall. The i.r. spectra of the two samples were identical.

Examination of the original reaction mixture by g.l.c. for the presence of nitroethane showed no evidence for this compound.

This reaction proved useful for the preparation of diethyl *o*-nitrophenylphosphonate on a larger scale. Thus, the reaction of *o*-dinitrobenzene (14.15 g., 84 m. mole) and triethyl phosphite (60.25 g., 363 m. mole) gave diethyl *o*-nitrophenylphosphonate (15.21 g., 59 m. mole, 70%), together with the excess of triethyl phosphite (35.33 g., 213 m. mole), triethyl phosphate (12.70 g., 70 m. mole), and ethyl nitrite (3.0 g.. 40 m. mole, 48%).

Under these somewhat vigorous conditions, triethyl phosphate was formed in appreciable amounts, suggesting that competing deoxygenation reactions were taking place. The large amount of tarry material formed was also indicative of side-reactions. The reaction was therefore repeated in a suitable solvent.

(b) Reactions in presence of a solvent. A solution of o-dinitrobenzene (5.0 g., 30 m. mole) and triethyl phosphite (7.76 g., 47 m. mole) in acetonitrile (20 ml.) was heated under reflux for 8 hours. After removal of the solvent under reduced pressure, distillation gave a trace only of triethyl phosphate, and, as the final fraction, diethyl o-nitrophenylphosphonate (6.07 g., 23 m. mole, 78%). Ethyl nitrite (1.13 g., 15 m. mole, 50%) was again recovered from the cold trap.

Under these conditions, large scale preparations could again be undertaken. A solution of o-dinitrobenzene (30.28 g., 180 m. mole) and triethyl phosphite (50.00 g., 300 m. mole) in acetonitrile (100 ml.) was heated under reflux for 8 hours. On removal of the solvent under reduced pressure, diethyl o-nitrophenylphosphonate, (16.8 g., 65 m. mole), crystallised out and could be collected by filtration. This was shown by g.l.c. to be a pure sample without further distillation. Distillation of the filtrate yielded a further quantity (19.6 g., 75 m. mole) of diethyl o-nitrophenylphosphonate (total yield 36.4 g., 140 m. mole, 78%).

In an attempt to reduce still further the amount of tarry material formed, the reaction was carried out by means of the Continuous Flow Procedure described by

Allen, Byers, Humphlett and Reynolds.[196] Solutions, in varying concentrations, of o-dinitrobenzene and triethyl phosphite in acetonitrile or dimethylformamide, were dropped on to a one-metre column packed with glass helices, maintained at a controlled temperature in the range 90-130°. The effluent from the column was recycled several times to improve the ratio of product to starting material, the progress of the reaction being followed by g.l.c.

Although reaction did take place to give diethyl o-nitrophenylphosphonate without the formation of any black tarry material, the method proved to be unsatisfactory in this case owing to the relative slowness of the reaction in the presence of solvent, and to the increasing viscosity of the reaction mixture in the absence of solvent. The low solubility and high melting point of o-dinitrobenzene were also unsuited to this potentially useful experimental method.

In order to determine the effect of light on this reaction, parallel reactions, with a 1:2 molar ratio of o-dinitrobenzene and triethyl phosphite in acetonitrile, were carried out in the dark at 90°, in the dark at 18°, and in the presence of u.v. light at 18°. The progress of each reaction was followed by g.l.c. relative to an

internal standard. After one hour at 90°, the reaction in the dark showed 65% loss of o-dinitrobenzene, while both reactions at 18° showed 5-7% loss of o-dinitrobenzene after 20 hours. It was concluded that there was no significant photolytic effect in this reaction.

Confirmation of the structure of diethyl o-nitrophenylphosphonate. A solution of diethyl o-nitrophenylphosphonate (2.08 g., 8.03 m. mole) in concentrated hydrochloric acid (20 ml.) was heated under reflux for 5 hours. The excess of acid was removed by distillation under reduced pressure and the resulting colourless solid dried in vacuo. Crystallisation from acetone-chloroform gave o-nitrophenylphosphonic acid, (1.54 g., 7.8 m. mole, 94%), m.p. 200-201°, (lit.[186] 200-203°). (Found: C, 35.6; H, 3.1; N, 6.2; P, 15.4. Calc. for $C_6H_6NO_5P$: C, 35.5; H, 2.95; N, 6.9; P, 15.3 %). Titration showed this to be a dibasic acid. (Found: mol. wt. = 203. Calc. for $C_6H_6NO_5P$, mol. wt. = 203.) The n.m.r. spectrum (D_2O) showed an aromatic multiplet only, centred at τ = 2.14. The u.v. spectrum (ethanol) showed λ_{max} = 250 mμ (ε = 3970); lit.[186] λ_{max} = 251 mμ (ε = 3740).

Later, an authentic sample of the phosphonic acid was kindly provided by Professor Freedman. The two

samples proved identical (melting point, mixed m.p., and i.r. spectrum).

Esterification of these two samples by reaction with ethanol in the presence of N,N'-dicyclohexyl-carbodi-imide[197] gave the same product in both cases. Thus, a solution of o-nitrophenylphosphonic acid (1.01 g., 5.05 m. mole), absolute ethanol (0.62 g., 13.5 m. mole), and N,N'-dicyclohexylcarbodi-imide (3.57 g., 17.3 m. mole) in pyridine (30 ml.) was allowed to stand at room temperature for 12 hours, and was then heated to 60° for a further 12 hours. Sufficient water was added to complete the precipitation of N,N'-dicyclohexylurea, which was then removed by filtration. After removal of the solvent under reduced pressure, the residue was redistilled to give, after recrystallisation from petroleum (b.p. 60-80°), diethyl o-nitrophenylphosphonate (1.02 g., 3.94 m. mole, 78%), m.p. 52-54°, mixed m.p. with the original ester 54°. The i.r. spectra were identical.

Reaction of o-dinitrobenzene with trimethyl phosphite.

This and subsequent reactions were carried out on a relatively large scale as the dialkyl arylphosphonates were required for preparative studies by other workers.

A solution of o-dinitrobenzene (23.69 g., 141 m. mole)

and trimethyl phosphite (35.60 g., 287 m. mole) in acetonitrile (100 ml.) was heated under reflux for 24 hours. After removal of the solvent and the excess of trimethyl phosphite by distillation under reduced pressure, the residue was distilled further to give a clear orange oil which crystallised readily as it cooled. The crystals were washed quickly with ether to remove traces of trimethyl phosphate and were then recrystallised from petroleum (b.p. 60-80°) to give fine colourless crystals of dimethyl o-nitrophenylphosphonate, (21.70 g., 94 m. mole, 67%), m.p. 79.5-80.5°. (Found: C, 41.6; H, 4.2; N, 6.4. $C_8H_{10}NO_5P$ requires C, 41.6; H, 4.4; N, 6.1 %).

The i.r. spectrum showed ν_{max}: (P = O), 1250; (P-O-Me), 1070-1040 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed P-OCH_3, doublet, 6H, τ = 6.15; and aromatic, multiplet, 4H, centred at τ = 2.24.

A solution of dimethyl o-nitrophenylphosphonate (1.75g., 7.56 m. mole) in an excess of concentrated hydrochloric acid (15 ml.) was heated under reflux for five hours. After removal of the excess of acid under reduced pressure, the residue was dried at 70°/0.05 mm. and recrystallised from acetone-chloroform to give o-nitrophenylphosphonic acid (1.07 g., 5.2 m. mole, 68%),

m.p. 199-201°, and mixed m.p. with an authentic sample, 199-202°.

Reaction of o-dinitrobenzene with tri-isopropyl phosphite. In a similar manner, the reaction of o-dinitrobenzene (7.34g., 43.6 m. mole) and tri-isopropyl phosphite (36.08 g., 173 m. mole) in acetonitrile (100 ml.) gave di-isopropyl o-nitrophenylphosphonate (6.72 g., 23.4 m. mole, 54%), b.p. 113°/0.02 mm. (Found: C, 50.1; H, 6.4; N, 5.1; P, 10.9 %. Mol. wt. = 280. $C_{12}H_{18}NO_5P$ requires C, 50.2; H, 6.3; N, 4.9; P, 10.8 %. Mol. wt. = 287).

The i.r. spectrum showed ν_{max}: (P-O-Pr^i), 950-1010, 1095, 1132, 1170; (P = O), 1248 cm^{-1}. The H^1 n.m.r. spectrum (carbon tetrachloride) showed $P\cdot OCH(\underline{CH_3})_2$, triplet, 12H, τ = 8.65; $P\cdot O\underline{CH}(CH_3)_2$, sextet (due to overlapping), 2H, τ = 5.20; and aromatic, multiplet, 4H, centred at τ = 2.20. The P^{31} n.m.r. spectrum (ethanol) showed a complex band at δ = -8.5 p.p.m. relative to 85% phosphoric acid (external standard), again indicating that the phosphorus atom was bonded directly to the aromatic ring.

Acid hydrolysis of the ester, as described in previous experiments, gave o-nitrophenylphosphonic acid.

Reaction of o-dinitrobenzene with diethyl methylphosphonite. A solution of o-dinitrobenzene (6.15 g., 37.1 m. mole) and diethyl methylphosphonite (9.20 g., 67.6 m. mole) in acetonitrile (120 ml.) gave, after 20 hours at 18°, ethyl methyl-o-nitrophenylphosphinate, (6.50 g., 28.4 m. mole, 77%), b.p. 130°/0.01 mm. (Found: C, 47.0; H, 5.4; N, 6.2. $C_9H_{12}NO_4P$ requires C, 47.1; H, 5.2; N, 6.1 %).

The i.r. spectrum showed ν_{max}: (P-Me), 885-900, 1300; (P=O), 1225; (P-O-Et), 940-980, 1070-1050 and 1170 cm^{-1}. The n.m.r. spectrum (carbon tetrachloride) showed P·CH_3, doublet, 3H, τ = 8.15; P·OCH_2CH_3, triplet, 3H, τ = 8.75; P·OCH_2CH_3, quintet, 2H, τ = 6.0; and aromatic, multiplet, 4H, centred at τ = 2.2.

Acid hydrolysis as before gave methyl o-nitrophenylphosphinic acid, m.p. 154° (from chloroform), (Found: C, 41.4; H, 4.2; N, 6.9. $C_7H_8NO_4P$ requires C, 41.8; H. 4.0; N, 7.0 %). Titration showed this to be a monobasic acid. (Found: mol. wt. = 210. $C_7H_8NO_4P$ requires mol. wt. = 201.) The i.r. spectrum showed no evidence for the presence of (P-O-Et) groups. The n.m.r. spectrum (deuterochloroform) showed P·CH_3, doublet, 3H, τ = 8.17; and aromatic, multiplet, 4H, τ = 2.0-2.4.

Reaction of o-dinitrobenzene with O-sodium diethyl phosphite. o-Dinitrobenzene (1.00 g., 5.95 m. mole) and O-sodium diethyl phosphite (0.95 g., 5.94 m. mole), prepared by the reaction of diethyl phosphite dissolved in dry ether with sodium,[198] gave a red solution in acetonitrile (10 ml.) which darkened rapidly during heating under reflux. Examination of this reaction mixture after 4 hours by g.l.c. indicated that diethyl o-nitrophenylphosphonate was formed, but not as a major product. Removal of the solvent under reduced pressure gave a quantity of tarry material. Distillation of this residue yielded diethyl o-nitrophenylphosphonate (0.15 g., 0.58 m. mole, 9.8%). The tarry material was not characterised further.

Reaction of o-dinitrobenzene with ethyl diphenylphosphinite. A solution of ethyl diphenylphosphinite (0.313 g., 1.36 m. mole) in dimethylformamide (1 ml.) was added to a solution of o-dinitrobenzene (0.156 g., 0.93 m. mole) in dimethylformamide (1.5 ml.). The resulting fine colourless precipitate was separated from the clear orange solution by filtration, and recrystallised from ether-light petroleum to give diphenyl-o-nitrophenylphosphine oxide (0.084 g., 0.26 m. mole, 29%), m.p. 224-6°. (Found: C, 66.7; H, 4.4; N, 4.2; P, 9.6.

$C_{18}H_{14}NO_3P$ requires C, 66.9; H, 4.4; N, 4.3; P, 9.6 %).

The i.r. spectrum showed a great similarity to that of triphenylphosphine oxide, with additional absorption maxima at ν = 1522 and 1360 cm^{-1}., (NO_2). There was no evidence for the presence of (P-O-Et) groups. The n.m.r. spectrum showed an aromatic multiplet only, τ = 2.2-2.6, again similar to that of triphenylphosphine oxide.

A large scale preparation indicated that this reaction was strongly exothermic in solution at room temperature. Thus ethyl diphenylphosphinite (73.9 g., 321 m. mole) was added in small portions over $2\frac{1}{2}$ hours to a solution of o-dinitrobenzene (36.2 g., 216 m. mole) in dimethylformamide (95 ml.) at -10°. On removal of the ice-bath, the temperature of the reaction mixture rose to ca. 70°. After 12 hours at 18°, the precipitate that had formed was removed by filtration, washed with dimethylformamide and recrystallised from ether to give diphenyl-o-nitrophenylphosphine oxide (40.0 g., 124 m. mole, 57%), m.p. 227-8°. The filtrate was concentrated at reduced pressure and the residue chromatographed on alumina. Elution with benzene-light petroleum (1:1) gave o-dinitrobenzene (1.9 g., 11.6 m. mole), m.p. 110°; elution with benzene-ether (1:1)

gave ethyl diphenylphosphinate (4.1 g., 16.7 m. mole), m.p. 20-22°; and elution with ether gave further diphenyl-o-nitrophenylphosphine oxide [total yield 42.3 g., 132 m. mole, 65%, (based on reacted o-dinitrobenzene)]. Identification of the fractions was achieved by comparison with authentic samples.

Diphenyl-o-nitrophenylphosphine oxide was further characterised by reduction to the corresponding amino-compound. Diphenyl-o-nitrophenylphosphine oxide (2.01 g., 6.23 m. mole) was heated for 24 hours under reflux with a suspension of iron powder (1.5 g.) in ethanol (25 ml.), water (25 ml.) and concentrated hydrochloric acid (0.1 ml.). The hot reaction mixture was filtered through celite and then allowed to cool. The fine colourless precipitate which formed was removed by filtration and recrystallised from benzene to give diphenyl-o-aminophenylphosphine oxide (1.65g., 5.64 m. mole, 91%), m.p. 163-4°. (Found: C, 73.7; H, 5.4; N, 4.9. $C_{18}H_{16}NOP$ requires C, 73.7; H, 5.5; N, 4.8%). The i.r. spectrum showed ν_{max}: (NH_2), 3215, 3315, 3400 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed NH_2, broad peak, 2H, τ = 4.65; and aromatic, complex multiplet, 14H, τ = 2.6-3.0.

Reaction of o-dinitrobenzene with tri-n-butylphosphine. Tri-n-butylphosphine (3.53g., 17.4 m. mole) was added to a solution of o-dinitrobenzene (2.92 g., 17.4 m. mole) in acetonitrile (5 ml.), at 18°. An exothermic reaction took place during which the solution rapidly darkened. After 2 hours at 18°, the solvent was removed under reduced pressure to give a residual orange-brown oil, which exploded violently on attempted distillation.

The experiment was repeated with similar quantities of reagents as before. An attempt to separate the components of the residual oil by chromatography proved unsuccessful, unchanged o-dinitrobenzene being the only recognisable fraction.

Reaction of o-dinitrobenzene with triphenylphosphine. This reaction in the absence of solvent was expected to be unduly vigorous and was therefore not attempted.

A solution of o-dinitrobenzene (15.0 g., 89 m. mole) and triphenylphosphine (47.0 g., 179 m. mole) in toluene (100 ml.) was heated under reflux for 4 hours. Volatile products were collected in a liquid-air cold-trap as before. A reaction took place as the temperature of the reaction mixture reached 90-95°, with the evolution of a gas which collected in the cold-trap. The reaction

mixture, on cooling, gave a black precipitate, which, after separation and washing with ether, proved to be largely triphenylphosphine oxide (22.5 g., 81 m. mole), m.p. 150-155°, mixed m.p. with an authentic sample, 153-157°, together with some tarry material. No other product could be identified from the reaction mixture.

The cold-trap contained a colourless solid which, on exposure to air (the reaction having been carried out under nitrogen as usual), and as its temperature slowly rose to 18°, turned pale blue, then deeper blue, changed to a greenish liquid, and eventually gave off red fumes. This is typical of the behaviour of nitric oxide under such conditions.[199] The gas was not however further characterised.

The reaction was repeated with varying proportions of reagents and solvent. However, triphenylphosphine oxide was the only product isolated, in each case, from the black, intractable tars which formed the greater part of the reaction mixture.

Reaction of m-dinitrobenzene with triethyl phosphite. m-Dinitrobenzene (10.05 g., 60 m. mole) and triethyl phosphite (40.26 g., 240 m. mole) were heated together under reflux, as described previously, with a cold-trap to collect any volatile reaction products. A violent

reaction took place as the temperature of the reaction mixture reached 90-95°, to give a dark brown solution. After 1 hour at 100°, the reaction mixture was allowed to cool to 18° and was then distilled under reduced pressure. After removal of triethyl phosphite and triethyl phosphate, the dark residue decomposed vigorously on further heating to give a series of dark brown tarry products. From these, only a trace of unchanged m-dinitrobenzene could be identified. An examination of the reaction mixture by t.l.c. and g.l.c. suggested that 8-10 different products had been formed in this reaction, with no product obviously predominating. No volatile products were collected in the cold-trap.

Reaction of p-dinitrobenzene with triethyl phosphite. p-Dinitrobenzene (12.0 g., 72 m. mole) and triethyl phosphite (60.3 g., 364 m. mole) were heated together in the absence of a solvent. As the temperature of the reaction mixture reached 90-95°, there was a violent reaction with extensive decomposition. The experiment was temporarily abandoned.

A small-scale experiment, followed by g.l.c. confirmed that p-dinitrobenzene was rapidly consumed in the course of the reaction. The reaction was noticeably exothermic even on a 4-10 m. mole scale. The g.l.c.

analysis of the reaction mixture showed that a number of volatile products had been formed, all in very low yield (2-10%). No major product was observed under these g.l.c. conditions (2% N.P.G.S. at 200°).

The same reagents dissolved in acetonitrile or dimethylformamide showed no evidence of reaction after 8 hours under reflux, other than a darkening of the solution.

The reaction mixtures were examined by g.l.c. for the presence of diethyl p-nitrophenylphosphonate, by comparison with an authentic sample. There was no evidence for the presence of this compound as a major product of the reaction. Equally, with a wide range of unidentified products with similar boiling points and g.l.c. retention times, the possibility of the presence of diethyl p-nitrophenylphosphonate in a yield of 1-5% could not be excluded.

Reaction of p-dinitrobenzene with trimethyl phosphite. A solution of p-dinitrobenzene (0.41 g., 2.4 m. mole) and trimethyl phosphite (2.50 g., 20.1 m. mole) in acetonitrile (4 ml.) was heated under reflux for 8 hours. Samples were taken from this reaction mixture at intervals of one hour for g.l.c. examination. Over this period there was no loss of starting material

and no formation of any volatile product.

Reaction of p-dinitrobenzene with tri-isopropyl phosphite. A series of reactions similar in scale to that described above was carried out in acetonitrile or dimethylformamide as solvent. Although the reaction mixtures darkened on being heated under reflux, g.l.c. analysis indicated that there was little loss of starting material over a period of 8 hours. Removal of the solvent and volatile reagents by distillation under reduced pressure, and of the tarry material by washing with ether and by recrystallisation of the residue, led to the recovery of unchanged p-dinitrobenzene in 75-80% yield.

Reaction of p-dinitrobenzene with ethyl diphenylphosphinite. A solution of p-dinitrobenzene (5.0 g., 30 m. mole) and ethyl diphenylphosphinite (10.0 g., 43 m. mole) in dimethylformamide (40 ml.) was warmed gently. The yellow solution darkened through orange and red to black at 60°. As the temperature of the solution reached 100°, an exothermic reaction occurred and the solvent boiled. The reaction mixture was then maintained at 100° for a further 2 hours.

After removal of the solvent under reduced pressure, the tarry residue was adsorbed on to alumina and then

eluted quickly with ether. This procedure proved useful in a number of cases for the extraction of products and unchanged starting materials from the viscous tars and polymeric materials formed in the course of these reactions.

Vacuum distillation gave, as two readily separable fractions, unchanged p-dinitrobenzene (2.1 g., 12.5 m. mole, 42%, subl. 110-115°/0.02 mm., m.p. 172-3°, and ethyl diphenylphosphinate (5.4 g., 22 m. mole), b.p. 130-133°/0.02 mm., identified by comparison of their i.r. spectra with those of authentic samples. No other products could be identified from this reaction.

Reaction of p-dinitrobenzene with diethyl methylphosphonite. A solution of p-dinitrobenzene (6.35 g., 38 m. mole) and diethyl methylphosphonite (21.61 g., 159 m. mole) in acetonitrile (25 ml.) was heated under reflux for 12 hours to give a dark reaction mixture.

After removal of the solvent under reduced pressure, the residue was distilled further in vacuo. Examination of the distillation fractions by g.l.c. indicated that p-dinitrobenzene had been completely consumed in this reaction, but that the products formed were not separable by distillation. The fractions were therefore recombined and chromatographed on alumina.

Elution with petroleum ether (b.p. 40-60°) gave fine colourless crystals of p-nitrophenetole (0.20 g., 1.2 m. mole, 3.2%), m.p. 52-53°, (lit.[179] 57-58°). The i.r. spectrum[201] and the n.m.r. spectrum[203] [(carbon tetrachloride), O·CH_2CH_3, triplet, 3H, τ= 8.62; O·CH_2CH_3, quartet, 2H, τ= 5.88; aromatic, 2 doublets, 4H, τ= 1.85 and 3.15.] were identical with those published for this compound.

Elution with benzene-ether (1:1) gave yellow crystals of N-ethyl-p-nitroaniline (0.12 g., 0.73 m. mole, 1.9%). m.p. 88-90°, (lit.[179] 96°), identified by comparison with an authentic sample. The i.r. spectrum showed ν_{max}: (N-H), 3320 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed N·CH_2CH_3, triplet, 3H, τ= 8.70; N·CH_2CH_3, quartet, 2H, τ= 6.72; NH, broad singlet, 1H, τ= 5.4; aromatic, 2 doublets, 4H, τ= 1.94 and 3.50.

Ether eluted, as fine yellow needles, p-nitroaniline, (0.45 g., 3.26 m. mole, 8.6%), (lit.[179] 146°), identified by comparison of the i.r. and n.m.r. spectra with those of an authentic sample, mixed m.p. 144-146°. No other fractions could be identified.

Reaction of 1,2,4-trinitrobenzene with triethyl phosphite. A solution of triethyl phosphite (5.3 g.,

31.6 m. mole) in dimethylformamide (20 ml.) was added slowly to a solution of 1,2,4-trinitrobenzene (3.0 g., 14.1 m. mole) in dimethylformamide (20 ml.) at 0°. On removal of the ice-bath at the completion of this addition, the temperature of the reaction mixture rose to 30-35°.

The solvent and the excess of triethyl phosphite were removed by distillation under reduced pressure. Further distillation of the residue gave, as the final fraction, diethyl 2,4-dinitrophenylphosphonate (2.3 g., 7.6 m. mole, 54%), b.p. 155°/0.01 mm. (Found: C, 39.8; H, 4.4; N, 9.2. $C_{10}H_{13}N_2O_7P$ requires C, 39.5; H, 4.3; N, 9.2 %).

The i.r. spectrum showed ν_{max}: (NO_2), 1550, 1350; (P=O), 1260; (P-O-Et), 945-980, 1010-1050, 1162 cm^{-1}. The n.m.r. spectrum (carbon tetrachloride) showed P-$OCH_2\underline{CH_3}$, triplet, 6H, τ= 8.6; P-$OCH_2\underline{CH_3}$, quintet, 4H, τ= 5.80; and aromatic, multiplet, 3H, τ= 1.3-1.9.

The formulation of this as the 2,4-dinitro-isomer, rather than the 2,5-dinitro- or the 3,4-dinitro-isomer, depended on an analysis of the n.m.r. aromatic multiplet, which will be discussed further in a later chapter, and upon the isolation of the same isomer from the reaction of chloro-2,4-dinitrobenzene and triethyl phosphite,

also described later.

During the course of the distillation of this product from the reaction residue, a fine yellow sublimate had formed at 100-120°/0.01 mm. After purification by further sublimation, this was identified as 2,4-dinitrophenol (0.15 g., 0.82 m. mole, 5.8%), m.p. 108-110° (lit.[203] m.p. 113°), by comparison of the i.r. and n.m.r. spectra with those of an authentic sample, mixed m.p. 109-110°.

An attempt to carry out this reaction in the absence of a solvent, on a very small scale, demonstrated that the reaction was extremely exothermic and liable to be violent under these conditions.

Reaction of 1,2,4-trinitrobenzene with trimethyl phosphite. A solution of 1,2,4-trinitrobenzene (2.0 g., 9.5 m. mole) and trimethyl phosphite (2.0 g., 16.2 m. mole) in acetonitrile (25 ml.) was warmed gently to 60° and maintained at this temperature for one hour. The solvent was removed under reduced pressure and the residue washed through a column of silica gel with ether to remove the tarry products formed.

Distillation of this purified material gave a yellow oil, b.p. 132-5°/0.01 mm., which crystallised on cooling. Recrystallisation from ether-light petroleum

gave dimethyl 2,4-dinitrophenylphosphonate (1.9 g., 6.9 m. mole, 73%), m.p. 70-73°. (Found: C, 34.7; H, 3.0; N, 9.9. $C_8H_9N_2O_7P$ requires C, 34.8; H, 3.3; N, 10.3 %).

The i.r. spectrum showed ν_{max}: (P-O-Me), 1020-1060; (P=O), 1260; and (NO_2), 1350 and 1540 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed P-OCH_3, doublet, 6H, τ= 6.08; and aromatic, multiplet, 3H, τ= 1.2-1.8. A complete analysis of this aromatic multiplet was possible and will be described in a later chapter.

Reaction of 1,2,4-trinitrobenzene with tri-isopropyl phosphite. In a similar manner, 1,2,4-trinitrobenzene (2.0 g., 9.5 m. mole) and tri-isopropyl phosphite (2.8 g., 13.4 m. mole) in acetonitrile (25 ml.) gave di-isopropyl 2,4-dinitrophenylphosphonate (1.51 g., 4.55 m. mole, 48%), m.p. 37-8°. (Found: C, 43.4; H, 5.4; N, 8.2. $C_{12}H_{17}N_2O_7P$ requires C, 43.4; H, 5.1; N, 8.4 %).

The i.r. spectrum showed ν_{max}: (P-O-Pr^i), 970-1010, 1100, 1135, 1175; and (P=O), 1255 cm^{-1}. The n.m.r. spectrum showed P-$OCH(CH_3)_2$, triplet, 12H, τ= 8.62; P-$OCH(CH_3)_2$, sextet (due to overlapping), 2H, τ = 5.12; and aromatic, multiplet, 3H, τ= 1.3-1.8.

Reaction of 1,2,4-trinitrobenzene with ethyl diphenylphosphinite. This reaction proved to be highly

exothermic, even in solution at low temperatures. A solution of ethyl diphenylphosphinite (6.0 g., 26.0 m. mole) in dimethylformamide (25 ml.) was added dropwise to a semi-solid solution of 1,2,4-dinitrobenzene (2.0 g., 9.4 m.mole) in dimethylformamide at -60°. A vigorous reaction took place and, despite continued cooling, the temperature of the reaction mixture rose to +60°, with a considerable evolution of nitrous fumes, to give a black, tarry reaction mixture.

Distillation and chromatography gave no identifiable products, it being impossible to separate the many products, in low yield, from the polymeric tars.

Reaction of 1,2,4-trinitrobenzene with triphenylphosphine. A similar difficulty to the above was experienced in this reaction. A solution of 1,2,4-trinitrobenzene (0.36 g., 1.69 m. mole) and triphenylphosphine (2.35 g., 8.96 m. mole) in acetonitrile (50 ml.) on gentle warming, gave a dark solution and nitrous fumes. Triphenylphosphine oxide (1.12 g., 4.03 m. mole, 45%), m.p. 150-1°, (lit[5] m.p. 152-3°), identified by comparison of the i.r. spectrum with that of an authentic sample, was the only product isolated from the tarry residue.

Reaction of nitrobenzene with ethyl diphenylphosphinite. A solution of nitrobenzene (0.21 g., 1.71 m. mole) and ethyl diphenylphosphinite (0.41 g., 1.76 m. mole) in dimethylformamide (5 ml.) was heated under reflux for 6 hours. The black, tarry reaction mixture was examined by t.l.c. for the presence of triphenylphosphine oxide. No evidence for the presence of this was found.

Reaction of nitrobenzene with triethyl phosphite. A solution of nitrobenzene (1.23 g., 10 m. mole) in triethyl phosphite (8.3 g., 50 m. mole) was heated under reflux for 6 hours. The solution became increasingly dark and viscous. The reaction mixture was examined by g.l.c. for the presence of diethyl phenylphosphonate, an authentic sample of this being available: there was no evidence, however, for the presence of this compound. Distillation and chromatography failed to separate identifiable fractions from the quantities of tarry material formed.

Reaction of o-nitrobenzenediazonium fluoroborate with triethyl phosphite. A solution of triethyl phosphite (17.1 g., 104 m. mole) in benzene (25 ml.) was added slowly to a solution of o-nitrobenzenediazonium fluoroborate (6.2 g., 22 m. mole) in benzene (50 ml.) at 18°.

A vigorous exothermic decomposition took place to give a clear red solution.

After removal of the solvent under reduced pressure, examination of the residue by g.l.c. indicated that 8-10 volatile substances had been formed in yields of 5-15%, with no product predominating. Comparison of the chromatogram of this reaction mixture with those of a series of authentic samples, on two different g.l.c. columns (2% N.P.G.S. and 3% Q.F.-1 at 160-185°), and by t.l.c. on silica, led to the identification of o-nitrobiphenyl (12-14%), o-nitroaniline (11%) and N-ethyl-o-nitroaniline (6%). There was no evidence for the formation of nitrobenzene or of o-nitrophenol.

Reaction of 4-methyl-2'-nitrodiphenylsulphone with triethyl phosphite. The reaction of triethyl phosphite (6.65 g., 40 m. mole) and 4-methyl-2'-nitrodiphenylsulphone (2.77 g., 10 m. mole) at 150° for 12 hours was reported to give a solid black tar, insoluble in all solvents except dimethylformamide, from which no products could be isolated.[200]

This reaction was repeated by heating a solution of 4-methyl-2'-nitrodiphenylsulphone (0.38 g., 1.37 m. mole) and triethyl phosphite (0.87 g., 5.18 m. mole) in acetonitrile (3ml.) under reflux for 10 hours. On

removal of the solvent by distillation under reduced pressure, a precipitate formed which was removed by filtration. After recrystallisation from chloroform, this was shown to be unchanged sulphone (0.10 g., 0.32 m. mole), by comparison of i.r. spectrum with that of an authentic sample.[200]

Both t.l.c. and g.l.c. analysis indicated that diethyl o-nitrophenylphosphonate was present in low yield. This was confirmed by chromatography on silica gel, ether eluting a fraction of almost pure diethyl o-nitrophenylphosphonate (0.022 g., 0.084 m. mole, 8%), identified by comparison of the i.r. spectrum with that of an authentic sample.

Reaction of 2-nitropyridine-N-oxide with triethyl phosphite. A solution of 2-nitropyridine-N-oxide (0.58 g., 4.28 m. mole) and triethyl phosphite (2.56 g., 15.3 m. mole) in acetonitrile (15 ml.) was heated under reflux for one hour to give a clear orange solution. After removal of the solvent under reduced pressure, the residue was distilled to give a yellow oil (0.903 g.), b.p. 80-120°/0.01 mm. Examination of this oil by g.l.c. showed it to be a mixture of triethyl phosphate, an unknown major product, and a number of minor products.

Chromatography on alumina gave, on elution with 1:1

benzene-ether, a yellow oil, (0.37 g.), which was shown by g.l.c. to be an impure sample of the major product. Further attempts to purify this sample by distillation and chromatography were unsuccessful. Preparative-scale g.l.c., however, gave, as a yellow oil, diethyl 2-pyridylphosphonate (total yield ca. 0.32 g., 1.49 m. mole, 35%), b.p. 110-120°/0.01 mm. (Found: C, 50.3; H, 6.4; N, 6.9. $C_9H_{14}NO_3P$ requires C, 50.3; H, 6.5; N, 6.5 %). [The corresponding N-oxide, $C_9H_{14}NO_4P$ would require C, 46.7; H, 6.05; N, 6.05 %]. The i.r. spectrum showed ν_{max}: (P=O), 1255; (P-O-Et), 970, 1020-1055, 1170. The n.m.r. spectrum (deuterochloroform) showed $POCH_2\underline{CH_3}$, triplet, 6H, τ= 8.6; $P\text{-}O\underline{CH_2}CH_3$, quintet, 4H, τ= 5.6; pyridine ring, multiplet, 4H, τ= 1.6-2.7.

Reaction of 2-nitropyridine and 4-nitropyridine-N-oxide with triethyl phosphite. Under similar reaction conditions to those described in the previous experiment, no reaction at all was observed between triethyl phosphite and either 2-nitropyridine or 4-nitropyridine-N-oxide. Examination of the reaction mixtures by g.l.c. indicated that the starting material remained unchanged after 8 hours of heating under reflux in acetonitrile. In the absence of solvent, and at high

temperatures, a reaction took place in each case to give a black intractable tar. No products were identified from these reactions.

Reaction of o-chloronitrobenzene with triethyl phosphite. o-Chloronitrobenzene (12.0 g., 76 m. mole) and triethyl phosphite (80.3 g., 478 m. mole) were heated under reflux, in the absence of solvent, for one hour. A liquid-air cold-trap was used as before to collect any volatile products from the reaction. There was no vigorous reaction of the kind that had occurred in the corresponding reaction of o-dinitrobenzene with triethyl phosphite, although the solution darkened rapidly at 80°.

A white solid, at -180°, collected in the cold-trap. This was identified as ethyl chloride (2.6 g., 40 m. mole, 53%) by comparison of the i.r., n.m.r., and mass-spectra with those of an authentic sample.[204]

The fate of the remainder of the molecule could not be determined. An examination of the reaction mixture by g.l.c. showed a number of high-boiling products in low yields. Distillation and repeated chromatography on alumina, and on silica gel, gave a series of yellow oils, all of which were, however, impure. No structural assignments could, therefore,

be made.

The experiment was repeated by heating a solution of o-chloronitrobenzene (10.50 g., 67 m. mole) and triethyl phosphite (16.60 g., 100 m. mole) in acetonitrile (30 ml.) under reflux for 8 hours, with a liquid-air cold-trap, as above. At the end of the reaction, ethyl chloride (0.40 g., 6 m. mole, 9.2%) dissolved in acetonitrile was again identified in the cold trap by comparison with an authentic sample.

Distillation and repeated chromatography of the reaction mixture led to the recovery of unchanged o-chloronitrobenzene (3.7 g., 24 m. mole), triethyl phosphite (6.1 g., 37 m. mole), and triethyl phosphate (2.55 g., 14 m. mole). The other products of this reaction could not be separated by either distillation or chromatography. Although g.l.c. analysis on one column (2% N.P.G.S. at 165°) did suggest that diethyl o-nitrophenylphosphonate might be present in low yield, this could not be confirmed by any other method.

Reaction of chloro-2,4-dinitrobenzene with triethyl phosphite. A solution of chloro-2,4-dinitrobenzene (10.10 g., 50 m. mole) and triethyl phosphite (33.15 g., 200 m. mole) in toluene (100 ml.) was heated under reflux for 6 hours. Examination of the reaction

mixture by g.l.c. showed that at least 9 "major" products had been formed in the course of this reaction, together with a number of subsidiary products.

After removal of the solvent under reduced pressure, the residue was distilled to give a clear orange oil. Chromatography of this oil on alumina (elution with 1:1 benzene-ether), and further chromatography of this fraction on silica (elution with ether) gave a pure sample of diethyl 2,4-dinitrophenylphosphonate (0.17 g., 5.6 m. mole, 11.2%), a sample of which was available from an earlier experiment. The i.r., n.m.r., and g.l.c. characteristics of the two samples were identical.

No further components of this reaction mixture could be isolated in sufficient purity for any structure to be assigned.

3. Reaction of o-Alkylnitroso- and Alkylnitrobenzenes with Tervalent Phosphorus Reagents.

In this series of experiments, in contrast to those described in the previous chapter, authentic samples of the products of the reactions were generally available or could be synthesised by known methods: identification was therefore possible by means of a direct comparison of the i.r. and n.m.r. spectra in each case. The spectra are described in a later

chapter, where necessary, and are not included in the experimental details. The spectra of other, novel, compounds are described in the appropriate place in the text.

Reaction of o-nitrosotoluene with triethyl phosphite. (a) Reaction in hydrocarbon solvent. A solution of o-nitrosotoluene (2.42 g., 20 m. mole) in benzene (30 ml.) was added slowly to a solution of triethyl phosphite (3.32 g., 20 m. mole) in benzene (40 ml.) at 0°. The solution changed colour from blue-green, to pale green, to orange. After one hour, g.l.c. examination of the reaction mixture showed that the major product was 2,2'-dimethylazoxybenzene, together with smaller amounts of other products.

The solvent was removed under reduced pressure and the residue subjected to chromatography on alumina. Elution with 1:1 benzene-light petroleum (b.p. 40-60°) gave a pure sample of 2,2'-dimethylazoxybenzene (1.08 g., 4.6 m. mole, 46%), m.p. 55-56°. (lit.[174] 59°). Elution with benzene gave o-toluidine (0.15 g., 1.4 m. mole, 7%). The i.r. and n.m.r. spectra of both compounds were identical with those of authentic samples.

An examination of the original reaction mixture

by g.l.c.-i.r. collection and analysis led to the identification of a minor product of the reaction as N-o-tolyl-2-acetimidylpyridine (3-5%), an authentic sample of which had been prepared by the method of Sundberg,[73] by heating o-toluidine (1.0 g., 9.3 m. mole) and 2-acetylpyridine (1.0 g., 8.3 m. mole) at 200° for 2 hours in the presence of a trace of zinc chloride.

A second minor product was isolated by the same technique and identified as diethyl N-o-tolylphosphoramidate (ca. 5%) by comparison of the i.r. spectrum and the g.l.c. retention time with those of an authentic sample.

(b) Reaction in triethyl phosphate solution, with a large excess of triethyl phosphite. A solution of o-nitrosotoluene (9.90 g., 82 m. mole) in triethyl phosphate (35 ml.) was added in small portions to triethyl phosphite (75 ml.) at 0°. The original green colour of the solution changed through yellow to a dark brown. The reaction proved to be extremely exothermic, and, despite stirring and cooling in an ice-bath, the reaction temperature tended to rise above 20°.

An examination of the reaction mixture by g.l.c. and g.l.c.-i.r. collection and analysis showed that the anil, N-o-tolyl-2-acetimidylpyridine (21%), and triethyl

N-o-tolylphosphorimidate and/or diethyl N-ethyl-N-o-tolylphosphoramidate and/or diethyl N-o-tolylphosphoramidate, (total yield ca. 32%), had been formed at the expense of 2,2'-dimethylazoxybenzene (ca. 9%). Two small peaks corresponding to high boiling products (ca. 3%) were not identified.

> In this and in subsequent experiments it is difficult to give precise yields of trialkyl N-arylphosphorimidates and dialkyl N-alkyl-N-arylphosphoramidates, on the basis of g.l.c. alone, as rearrangement from the first to the second takes place readily on distillation or on injection on to a g.l.c. column. Dialkyl N-arylphosphoramidates are also formed to a lesser extent on a g.l.c. column, from the corresponding trialkyl N-arylphosphorimidates, and to a much greater extent by hydrolysis during chromatography on a column of alumina or silica gel. This problem will be discussed further in a later chapter.

The reaction mixture from the above experiment was distilled under reduced pressure to remove the excess of triethyl phosphite and the triethyl phosphate solvent, and the gummy residue washed with light petroleum. Well-formed crystals of diethyl N-o-tolylphosphoramidate

(2.1 g., 8.6 m. mole, 10.5%), m.p. 93.5° (lit.[200] 95°), were separated from the residue, and identified by comparison with an authentic sample. The n.m.r. spectrum of the residue (5.10 g.) showed it to be a mixture of the anil, N-o-tolyl-2-acetimidylpyridine (ca. 1.55 g., 7.4 m. mole, 18%) and triethyl N-o-tolylphosphorimidate (ca. 3.55 g., 13.1 m. mole, 16%).

Chromatography of the residue on a column of alumina gave two identifiable fractions. Elution with 1:1 benzene-light petroleum b.p. 40-60°) gave 2,2'-dimethylazoxybenzene (0.21 g., 1.27 m. mole, 3.1%), m.p. 55-57°, (lit.[174] 59°). Elution with 1:1 benzene-ether gave diethyl N-o-tolylphosphoramidate (1.83 g., 7.5 m. mole, 9.1%), m.p. 93-94° (lit.[200] 95°). The anil was not found in any of the fractions following the chromatography.

Sundberg[73] reported the isolation of N-o-tolyl-α-methyl-α-2-pyridylnitrone as a yellow crystalline solid, m.p. 119-122°, from the reaction of o-nitroso-toluene with triethyl phosphite under the conditions described above. However there was no evidence for the formation of this compound in this experiment. An attempt to prepare an authentic sample of the nitrone from o-tolylhydroxylamine and 2-acetylpyridine gave

largely N-o-tolyl-2-acetimidylpyridine.

Reaction of o-ethylnitrosobenzene with triethyl phosphite. (a) Reaction in hydrocarbon solvent. A solution of o-ethylnitrosobenzene (1.36 g., 10 m. mole) in benzene (15 ml.) was added slowly to a solution of triethyl phosphite (1.67 g., 10 m. mole) in benzene (20 ml.) at 0°. The blue-green solution became pale-green, then orange. After one hour, a g.l.c. examination of the reaction mixture showed that the major product was 2,2'-diethylazoxybenzene, together with smaller amounts of other products. After removal of the solvent under reduced pressure, a portion (50%) of the residue was subjected to chromatography on alumina, the following fractions being collected:

1. orange oil (0.014 g.), eluted with light petroleum;
2. yellow crystalline solid (0.312 g.), eluted with 1:1 light petroleum-benzene;
3. orange oil (0.043 g.), eluted with benzene;
4. dark oils (0.058 g.), eluted with 1:1 benzene-ether;
5. red viscous oils (0.263 g.), eluted with 1:1 ether-methanol.

Fraction 2 was shown to be 2,2'-diethylazoxybenzene

(2.45 m. mole, 49%), m.p. ca. 18° (lit.[173] 13°). Fraction 3 was shown to be o-ethylaniline (0.36 m. mole, 7.2%). Fraction 5 was largely triethyl phosphate, together with some tarry material. Identification was achieved by comparison of the i.r. and n.m.r. spectra with those of authentic samples, in each case. Fraction 4 was thought to contain a trace of diethyl N-o-ethylphenylphosphoramidate, on the basis of g.l.c. examination, but this could not be obtained in sufficient purity for a positive identification. There was no evidence for the presence of N,2-diethylaniline, indoline or 2-propionylpyridine in any of the fractions collected.

By analogy with the reaction of o-nitrosotoluene with triethyl phosphite, it was expected that one of the trace products of the reaction of o-ethylnitrosobenzene with triethyl phosphite would be the corresponding anil, N-o-ethylphenyl-2-propionimidylpyridine. Accordingly, 2-propionylpyridine (5 g., 37 m. mole) b.p. 110-112°/14 mm., (lit.[205] 71-72°/5 mm.), prepared from 2-cyanopyridine and ethylmagnesium iodide by the method of La Forge[205], was heated under reflux with o-ethylaniline (5 g., 41 m. mole) in the presence of zinc chloride for 2 hours. Distillation of the reaction mixture gave N-o-ethylphenyl-2-propionimidylpyridine

(2.17 g., 9.1 m. mole, 25%), b.p. 100-102°/0.01 mm. (Found: C, 80.3; H, 7.5; N, 11.6. $C_{16}H_{18}N_2$ requires C, 80.6; H, 7.6; N, 11.8 %). The i.r. spectrum showed ν_{max}: (C=N), 1635 cm^{-1}. The n.m.r. spectrum (deuterochloroform) showed $Ar \cdot CH_2\underline{CH_3}$ and $\cdot N{:}C \cdot CH_2\underline{CH_3}$, overlapping triplets, 6H, τ= 8.80 and 8.92; $Ar \cdot \underline{CH_2}CH_3$ and $\cdot N{:}C \cdot \underline{CH_2}CH_3$, overlapping quartets, 4H, τ= 7.15 and 7.50, and a complex multiplet, 8H, τ= 1.3-3.4, similar to that in the spectrum of N-o-tolyl-2-acetimidylpyridine.

An examination of the original reaction mixture of the reaction of o-ethylnitrosobenzene and triethyl phosphite in benzene by g.l.c.-i.r. collection and analysis showed one of the minor products to be this anil, N-o-ethylphenyl-2-propionimidylpyridine (5%), by comparison of the i.r. spectra and g.l.c. retention time with those of the authentic sample.

The experiment was repeated in the presence of triethyl N-o-ethylphenylphosphorimidate. A solution of o-ethylnitrosobenzene (1.35 g., 10 m. mole) in benzene (15 ml.) was added slowly to a solution of triethyl phosphite (1.66 g., 10 m. mole) and triethyl N-o-ethylphenylphosphorimidate (5.70 g., 20 m. mole) in benzene (20 ml.). The reaction mixture was analysed as before: two products were isolated by chromatography on alumina

and identified as 2,2'-diethylazoxybenzene (0.59 g., 2.3 m. mole, 46%) and diethyl N-o-ethylphenylphosphoramidate (4.64 g., 17 m. mole, 85%), by a comparison with authentic samples. Examination of the reaction by g.l.c. showed that the anil was present in similar yield to that described previously.

(b) Reaction in triethyl phosphate solution, with a large excess of triethyl phosphite. A solution of o-ethylnitrosobenzene (5.0 g., 37 m. mole) in triethyl phosphate (15 ml.) was added in small portions to triethyl phosphite (35 ml.) at 0°. A vigorous exothermic reaction took place as before to give the anil, N-o-ethylphenyl-2-propionimidylpyridine (ca. 19%), triethyl N-o-ethylphenylphosphorimidate (ca. 20.5%), diethyl N-o-ethylphenylphosphoramidate (9.1%) and 2,2'-diethylazoxybenzene (7%). The isolation of these products was as described in the previous experiment, and identification was by comparison of their i.r. and n.m.r. spectra with those of authentic samples.

Reaction of o-nitrotoluene with triethyl phosphite. A solution of o-nitrotoluene (27.4 g., 200 m. mole) in triethyl phosphite (133 g., 800 m. mole) was heated under reflux for 17 hours. After removal of the excess of triethyl phosphite, and triethyl phosphate, under

reduced pressure, the black viscous residue was distilled to give a clear distillate (25.5 g.) and an involatile tar (14.9 g.) The distillate was diluted with ether and extracted with 2N-hydrochloric acid (3 x 50 ml.). The acidic extract was made alkaline with solid sodium hydroxide, extracted with ether, and the ethereal extract in turn extracted with acid. After further neutralisation and extraction with ether, the final ethereal solution was concentrated, and subjected to chromatography on alumina. Elution with 1:1 methanol-ether gave, after distillation, diethyl 2-methyl-3H-azepin-7-ylphosphonate (4.0 g., 17 m. mole, 8.5%), b.p. 115-120°/0.02 mm. (lit.[200] 125-130°/0.03 mm.), n_D^{20} 1.5040. The i.r. and n.m.r. spectra were as described for this compound[200] and are discussed briefly in the next chapter.

The neutral fraction of the original distillate was redistilled. Well-formed crystals of diethyl N-o-tolylphosphoramidate (final yield 12.1 g., 50 m. mole, 25%), m.p. 93-94°, (lit.[200] 95°), slowly separated out from the yellow distillate, identified as diethyl N-ethyl-N-o-tolylphosphoramidate (6.9 g., 27 m. mole, 13.5%), b.p. 110-115°/0.01 mm. (lit.[200] 120-130°/0.03 mm.), by comparison with an authentic sample.

The n.m.r. spectrum and g.l.c. analysis of the neutral fraction showed that these were the only two components. Under these conditions, there was no evidence for the presence of triethyl N-o-tolylphosphorimidate in the final reaction mixture.

Reaction of o-nitrotoluene with trimethyl phosphite. A solution of o-nitrotoluene (27.4 g., 200 m. mole) in trimethyl phosphite (124 g., 1000 m. mole) was heated under reflux for 14 hours, during which the colour of the solution darkened steadily. Distillation of the reaction mixture gave a low boiling fraction (106.1 g.), b.p. 20-85°/14 mm., a high boiling fraction (22.4 g.), b.p. 57-112°/0.02 mm., and an intractable tar (6.6 g.).

The low boiling fractions were redistilled to give trimethyl phosphate (ca. 57.1 g., 408 m. mole, 41%), b.p. 81°/14 mm., (lit.[206] 79°/12 mm.), dimethyl methylphosphonate (ca. 38.6 g., 311 m. mole, 31%), b.p. 70°/14 mm., (lit.[178] 67°/12 mm.), and unchanged o-nitrotoluene (8.7 g., 63.5 m. mole, 32%), identified by comparison of their i.r. and n.m.r. spectra with those of authentic samples. The yields of each were determined by g.l.c. and n.m.r. analyses.

The high boiling fraction was diluted with ether and extracted with water. Removal of the water under

reduced pressure and redistillation of the residual oil gave dimethyl 2-methyl-3H-azepin-7-ylphosphonate (5.24 g., 24.4 m. mole, 17.8% based on reacted o-nitrotoluene), b.p. 105°/0.04 mm. (Found: C, 50.1; H, 6.8; N, 6.45. $C_9H_{14}NPO_3$ requires C, 50.2; H, 6.5; N, 6.5 %). The i.r. and n.m.r. spectra, upon which this assignment of structure depends, are described in the next chapter.

The main component of the high boiling fraction was dimethyl N-methyl-N-o-tolylphosphoramidate (9.4 g., 41.0 m. mole, 30% based on reacted o-nitrotoluene), b.p. 90-95°/0.03 mm., identified by comparison with an authentic sample. Examination of the fraction by g.l.c. and by i.r. analysis showed that dimethyl o-tolylphosphoramidate was also present in small yield. A few crystals of this compound (1.55 g., 7.2 m. mole, 5.3% based on reacted o-nitrotoluene), m.p. 109°, separated out from the yellow oil on standing.

No other products were indicated by g.l.c. analysis (3% Q.F.-1 at 150-220°).

Reaction of o-ethylnitrobenzene with triethyl phosphite. A solution of o-ethylnitrobenzene (6.04 g., 40.0 m. mole) in triethyl phosphite (26.60 g., 160 m. mole) was heated under reflux for 14 hours. After removal of

triethyl phosphite and phosphate under reduced pressure, the dark viscous residue was diluted with ether and extracted with 2N-hydrochloric acid (3 x 20 ml.). The acidic extract, on being made alkaline, gave a dark oil which was extracted with ether. After this extract had been dried over calcium chloride, it was concentrated and chromatographed over alumina. Elution with 1:1 methanol-ether, followed by distillation, gave diethyl 2-ethyl-3H-azepin-7-ylphosphonate (0.75 g., 2.92 m. mole, 7.3%), b.p. 103°/0.02 mm. (lit.[200] 120-130°/0.03 mm.), n_D^{20}1.5066, as a stable yellow oil. The i.r. and n.m.r. spectra were as described for this compound and are discussed briefly in the following chapter.

The neutral fraction was analysed as before, and was shown to be a mixture of diethyl N-ethyl-N-o-ethylphenylphosphoramidate (1.12 g., 3.88 m. mole, 9.7%), b.p. 101-103°/0.05 mm. (lit.[200] 92-94°/0.03 mm.), and diethyl N-o-ethylphenylphosphoramidate (2.39 g., 9.3 m. mole, 23.3%), m.p. 100-101° (lit.[200] 103-105°), by comparison of the i.r. and n.m.r. spectra with those of authentic samples. As before, there was an involatile tarry residue (2.72 g.) which could not be characterised further.

Reaction of p-ethylnitrobenzene with triethyl phosphite. A solution of p-ethylnitrobenzene (15.10 g., 100 m. mole) in triethyl phosphite (66.5 g., 400 m. mole) was heated under reflux for 14 hours. A liquid-air cold-trap was used as described earlier to collect any volatile products of the reaction. During the course of the reaction, a colourless solid, at -180°, collected in the cold trap: this was shown by fractional distillation and vapour-phase i.r. spectra to be pure ethylene (0.70 g., 25 m. mole) by comparison with an authentic sample and with published spectra.[207]

After removal of the excess of triethyl phosphite and other volatile products (55.3 g.) under reduced pressure, b.p. 45-95°/14 mm., the black residue was distilled further to give a clear orange distillate (16.10 g.), b.p. 40-120°/0.02 mm., and a black involatile tar (8.25 g.). A preliminary g.l.c. examination of the distillates indicated that the lower boiling fraction had one major component other than triethyl phosphite and phosphate, and that the higher boiling fraction consisted of diethyl N-ethyl-N-p-ethylphenylphosphoramidate and diethyl N-p-ethylphenylphosphoramidate, together with an unexpected new product in lesser amount. Two products in small yield (less than 10%) with relatively

long g.l.c. retention times (20-25 mins., 3% Q.F.-1., 210°) were not characterised further. A high boiling product in small yield only was thought to be the corresponding azepine: this was later confirmed.

Preparative-scale g.l.c. led to the isolation of four of these compounds. The lower boiling fraction was shown to contain N,N,4-triethylaniline as a colourless oil identified by comparison with an authentic sample,[208] together with triethyl phosphite and triethyl phosphate. The n.m.r. spectrum (deuterochloroform) showed $Ar\cdot CH_2\underline{CH_3}$ and $N\cdot CH_2\underline{CH_3}$, overlapping triplets, 9H, τ= 8.8 and 8.9; $Ar\cdot \underline{CH_2}CH_3$, quartet, 2H, τ= 7.45; $N\cdot \underline{CH_2}CH_3$, quartet, 4H, τ= 6.69; and aromatic, two doublets, 4H, τ= 2.95 and 3.39.

The unexpected product, a yellow oil, was shown to be diethyl p-ethylphenylphosphonate by comparison with an authentic sample, and with published data.[183] The i.r. spectrum showed ν_{max}: (P=O), 1250; (P-O-Et), 970, 1020-1055, 1165 cm^{-1}. The n.m.r. spectrum (carbon tetrachloride) showed $ArCH_2\underline{CH_3}$ and $P\cdot OCH_2\underline{CH_3}$, overlapping triplets, 9H, τ=8.7 and 8.75; $ArCH_2\underline{CH_3}$, quartet, 2H, τ= 7.30; $P\cdot OCH_2\underline{CH_3}$, quintet, 4H, τ= 5.90; and aromatic, multiplet, 4H, τ= 2.05-2.85.

The two major products were confirmed as diethyl

N-ethyl-N-p-ethylphenylphosphoramidate and diethyl N-p-ethylphenylphosphoramidate by comparison of their i.r. and n.m.r. spectra with those of authentic samples. The suspected azepine and other higher boiling products were either too involatile or too unstable to be isolated by preparative-scale g.l.c. under these conditions (10% A.P.L. at 210°).

The original distillate, now known to contain these compounds, together with triethyl phosphite and phosphate, was examined by n.m.r. and i.r. spectroscopy. There was no evidence for the presence of triethyl N-p-ethylphenylphosphorimidate: diethyl N-ethyl-N-p-ethylphenylphosphoramidate was however shown by n.m.r. spectroscopy to be present as a major component, prior to any possible rearrangement on the g.l.c. column. Total yields of the various components were determined by calculation from the n.m.r. spectra of the mixtures; by slow distillation into relatively pure samples (complete fractionation being impossible); and by g.l.c. analysis with an internal standard (trans-stilbene). Reasonable agreement was reached between these different methods.

The yields, based on p-ethylnitrobenzene (100 m. mole) were:- diethyl p-ethylphenylphosphonate

(5-7%), diethyl N-p-ethylphenylphosphoramidate (20-26%), and diethyl N-ethyl-N-p-ethylphenylphosphoramidate (21-23%). The azepine, diethyl 4-ethyl-3H-azepin-7-ylphosphonate, was not isolated in a pure form, but was shown to be present (ca. 3%) by comparison of the n.m.r. spectrum of the final distillation fraction (b.p. 120-125°/0.02 mm.) with that of the azepine dimethyl 4-methyl-3H-azepin-7-ylphosphonate, isolated in a later experiment.

The lower boiling fraction consisted of triethyl phosphite (13.3 g., 80 m. mole, 20%), triethyl phosphate (37.2 g., 220 m. mole, 52%) and N,N,4-triethylaniline (1.80 g., 10 m. mole, 10%).

Reaction of p-nitrotoluene with triethyl phosphite. As in the previous experiment, p-nitrotoluene (13.7 g., 100 m. mole) and triethyl phosphite (66.50 g., 400 m. mole) gave, after 14 hours under reflux, ethylene (0.55 g., 20 m. mole), diethyl p-tolylphosphonate (5%) diethyl N-ethyl-N-p-tolylphosphoramidate (24%), and diethyl N-p-tolylphosphoramidate (26%), identification being achieved by comparison of the i.r. and n.m.r. spectra with those of authentic samples. The azepine, diethyl 4-methyl-3H-azepin-7-ylphosphonate (6%) was again thought to be present from n.m.r. spectral evidence: it could

not however, be isolated in a pure state. Attempts to extract it from the reaction mixture failed to separate it from the other basic materials. Preparative scale g.l.c. failed to give a fraction corresponding to this compound.

The cold-trap condensate, largely ethylene, was examined by i.r. spectroscopy for the presence of ethyl nitrite: no evidence for the presence of this compound was found.

The experiment was repeated in the dark at 150°, and in the presence of u.v. light at 10°, to determine the effect of light upon the reaction. A 10:1 excess of triethyl phosphite was used in both cases.

In the dark, g.l.c. analysis showed that the reaction had followed the same path as before, giving the same products in similar yields. The yield of diethyl p-tolylphosphonate, in particular, was not affected by these conditions.

In the presence of u.v. light from the "Hanovia" lamp described earlier (in the preparation of dialkyl arylphosphonates) at 10° for 18 hours, the reaction followed a different path. Preparative-scale g.l.c. on a concentrated fraction of the reaction mixture showed three main components:- unchanged p-nitrotoluene,

diethyl N-p-tolylphosphoramidate, and an orange crystalline solid, m.p. 55-60°. The n.m.r. spectrum (deuterochloroform) of the latter compound showed a singlet (?), τ = 7.6 and an overlapping doublet, τ = 7.72 (J ~9 c/s); and aromatic, two doublets, τ = 2.1 and 3.4 (J ~9 c/s). The overall integral was ca. 5H:8H. The i.r. spectrum showed a sharp absorption at 2215 cm^{-1}. This product was not characterised further. There was no evidence for the formation of diethyl p-tolylphosphonate.

Reaction of p-nitrotoluene with trimethyl phosphite. p-Nitrotoluene (27.4 g., 200 m. mole) and trimethyl phosphite (124 g., 1000 m. mole) were heated together under reflux for 14 hours. Distillation of this reaction mixture under reduced pressure gave a low boiling fraction (120.2 g.), b.p. 20-90°/14 mm.; a high boiling fraction (15.13 g.), b.p. 50-110°/0.01 mm., and a tar (10.96 g.).

The low boiling fraction was shown by distillation and by g.l.c. analysis to be a mixture of trimethyl phosphate (ca. 63.3 g., 452 m. mole, 45%), dimethyl methylphosphonate (ca. 41.7 g., 336 m. mole, 34%), and unchanged p-nitrotoluene (ca. 7.2 g., 52.6 m. mole, 26%), by comparison of their i.r. and n.m.r. spectra

with those of authentic samples.

The high boiling fraction was shown by g.l.c. analysis to consist of 3 components only, two of which could be identified as dimethyl N-methyl-N-p-tolyl-phosphoramidate and dimethyl N-p-tolylphosphoramidate, by comparison with authentic samples. The distillate was diluted with ether and extracted with water. The unknown component was shown by g.l.c. to have been extracted completely by this method. The water was removed under reduced pressure to give an almost pure sample of dimethyl 4-methyl-3H-azonin-7-ylphosphonate (2.72 g., 12.7 m. mole, 8.6%) as a yellow oil. Redistillation gave the analytical sample, b.p. 110°/0.05 mm. (Found: C, 49.9; H, 6.4; N, 6.5. $C_9H_{14}NO_3P$ requires C, 50.3; H, 6.5; N, 6.5 %). The compound darkened on exposure to air and after 6 hours could no longer be satisfactorily analysed.

The i.r. spectrum showed ν_{max}: (P=O), 1255; (P-O-Me), 1020-1050, 1185 cm^{-1}. The n.m.r. spectrum (deuterochloroform), discussed in detail in the next chapter, showed C·CH_3, singlet, 3H, τ = 7.74; $-CH_2-$, doublet, 2H, τ = 7.44; P·OCH_3, doublet, 6H, τ = 6.2; and other $-CH=CH-$, multiplet, 3H, τ = 2.6-3.8.

The ethereal solution left after the aqueous

extraction was concentrated and redistilled to give a yellow oil, b.p. 95-105°/0.02 mm., from which colourless well-formed crystals slowly separated. The crystals were collected and shown to be dimethyl N-p-tolyl-phosphoramidate (1.7 g., 7.9 m. mole, 5.4%), m.p. 108-109°, while the oil was shown to be dimethyl N-methyl-N-p-tolylphosphoramidate (8.7 g., 38.0 m. mole, 26%), b.p. 100°/0.15 mm., (lit. [190] 100-101°/0.1 mm.), by comparison with authentic samples.

There was no evidence for the presence of trimethyl N-p-tolylphosphorimidate or dimethyl p-tolylphosphonate in the distillate from the reaction mixture.

Reaction of m-nitrotoluene with triethyl phosphite. m-Nitrotoluene (17.2 g., 125 m. mole) and triethyl phosphite (83.0 g., 500 m. mole) were heated together under reflux for 14 hours. A g.l.c. examination of the reaction mixture showed 2 major product peaks, corresponding to diethyl N-ethyl-N-m-tolylphosphoramidate (22%) and diethyl N-m-tolylphosphoramidate (27%). There was no evidence for any other high boiling products in significant yields.

Reaction of m-nitrotoluene with trimethyl phosphite. m-Nitrotoluene (17.2 g., 125 m. mole) and trimethyl phosphite (62.0 g., 500 m. mole) were heated together

under reflux for 14 hours. A g.l.c. examination of the reaction mixture showed that unchanged m-nitrotoluene (28%) was the major component. In addition to this, there were two products, with retention times corresponding to dimethyl N-methyl-N-m-tolylphosphoramidate (12%) and dimethyl N-m-tolylphosphoramidate (8.5%), and a further two unidentified products. There was no evidence for the presence of dimethyl m-tolylphosphonate.

After removal of the lower boiling materials under reduced pressure, the tarry residue was distilled further to give an orange distillate. Decomposition of the residue was observed before this distillation could be completed. Examination of the distillate by n.m.r. spectroscopy suggested that there might be two different azepines present in the mixture. Extraction, as described previously, failed to give a fraction of sufficient purity for further analysis.

Reaction of o-nitroanisole with trimethyl phosphite. o-Nitroanisole (19.14 g., 125 m. mole) and trimethyl phosphite (62.0 g., 500 m. mole) were heated together under reflux for 14 hours. A g.l.c. examination of the reaction mixture showed that unchanged o-nitroanisole (10%) remained in the solution. In addition

there were indications of four major products, corresponding to dimethyl 2-methoxyphenylphosphonate (2.5%), dimethyl N-methyl-N-o-methoxyphenylphosphoramidate (26%), dimethyl N-o-methoxyphenylphosphoramidate (12%), and an unidentified product, in lower yield.

Reaction of p-nitroanisole with trimethyl phosphite. p-Nitroanisole (19.14 g., 125 m. mole) and trimethyl phosphite (85.0 g., 690 m. mole) were heated under reflux for 14 hours. A g.l.c. examination of the reaction mixture showed that unchanged p-nitroanisole (25%) remained in the solution. In addition there were four main products, corresponding to dimethyl p-methoxyphenylphosphonate (3%), dimethyl N-methyl-N-p-methoxyphenylphosphoramidate (16%), dimethyl N-p-methoxyphenylphosphoramidate (13%), and a compound thought to be the corresponding azepine (15%).

Distillation and extraction as before confirmed these identities and yields. The azepine, dimethyl 4-methoxy-3H-azepin-7-ylphosphonate, b.p. 125-130°/ 0.05 mm., could not be obtained in analytical purity: the n.m.r. spectrum however, proved to be satisfactory.

Reaction of o-nitroanisole with triethyl phosphite.

o-Nitroanisole (1.91 g., 12.5 m. mole) and triethyl phosphite (8.4 g., 50 m. mole) were heated together under reflux for 14 hours. An attempt was made to examine the reaction mixture, by g.l.c. for the presence of diethyl o-methoxyphenylphosphonate. Unfortunately, under the g.l.c. conditions used (3% Q.F.—1, 2% N.P.G.S., 3% A.P.L., 165-190°) authentic samples of the phosphonate and of diethyl N-ethyl-N-o-methoxyphenylphosphoramidate had similar retention times, and it proved impossible to distinguish between these two products. No information could, therefore, be obtained from this experiment.

Reaction of p-nitroanisole with triethyl phosphite.

p-Nitroanisole (1.91 g., 12.5 m. mole) and triethyl phosphite (8.4 g., 50 m. mole) were heated together under reflux for 14 hours. An examination of the reaction mixture by g.l.c. showed 4 product peaks, corresponding to diethyl p-methoxyphenylphosphonate (6.0%), diethyl N-ethyl-N-p-methoxyphenylphosphoramidate (23%), diethyl N-p-methoxyphenylphosphoramidate (16%), and an unidentified product in low yield.

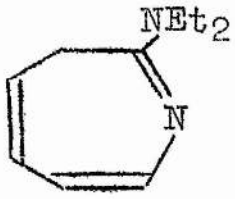
4. Spectral Data

(a) Nuclear magnetic resonance spectra

N.M.R. spectra have been recorded as described in the previous sections. In general the spectra obtained are as expected for the compounds, and no further discussion is required. The presence of the phosphorus atom in many of the products investigated leads to the observation of characteristically large coupling constants between phosphorus and the neighbouring protons. The presence of (P-OR) groups, in particular, is readily detectable by both n.m.r. and i.r. spectroscopy.

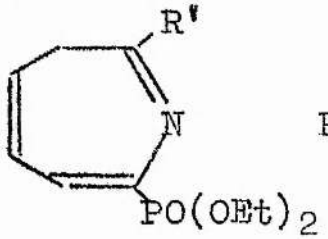
The spectra relating to compounds containing the azepine-ring system do, however, require further discussion in order to justify the formulation of these compounds as dialkyl 2- and 4-alkyl'-3H-azepin—7-ylphosphonates. Other structural problems will then be considered in turn, in the light of n.m.r. spectral evidence.

(i) n.m.r. spectra of products containing the azepine-ring system. Prior to this investigation, n.m.r. studies have been reported on a number of azepine systems, in particular on that azepine formed by the decomposition of phenyl azide in the presence of diethylamine;[119]



This compound was also isolated from the deoxygenation of nitrobenzene by diethyl methylphosphonite, in the presence of diethylamine.[200] In the reactions considered here, however, there is no base present other than the tervalent phosphorus compound used to effect the original deoxygenation. The n.m.r. spectra of the products obtained from the reaction of triethyl phosphite with o-nitrotoluene and o-ethylnitrobenzene, under these conditions, have been considered in detail by Todd.[200]

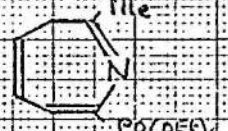
The products containing the azepine-ring now found in these reactions prove to be identical with those described and a re-examination of the spectral evidence confirms their formulation as the dialkyl 2-alkyl'-3H-azepin-7-ylphosphonates:

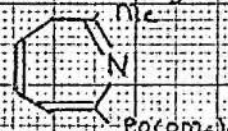


R' = Me, Et

The azepine from the reaction of o-nitrotoluene with triethyl phosphite. The n.m.r. spectrum in deuterochloroform of the relevant product from the reaction

n.m.r. spectra of azepines.





of triethyl phosphite with o-nitrotoluene shows a singlet, 3H, τ = 7.81; a quintet, 4H, τ = 5.85; and a triplet, 6H, τ = 8.66, which may be assigned to a tolyl methyl group and to two ethoxy groups attached to phosphorus. The ring protons appear as a quartet, 1H, H_A, τ = 2.98; a quintet, 1H, H_B, τ = 3.60; a quartet, 1H, H_C, τ = 4.52; and a doublet, 2H, H_D, τ = 7.46. Those parts of the spectrum relating to this ring system are shown opposite, together with the relevant portions of the spectra from the other azepines that have been isolated.

Scale expansion of the region from τ = 2.5 to τ = 5.0 reveals that each of the protons, H_A, H_B and H_C is coupled to some other nucleus, in addition to the adjacent protons. The additional coupling can only be with phosphorus, and examination of the expanded spectrum produces the following coupling constants (c/s):

$$J_{AB} = 6.0 \quad J_{BC} = 8.9 \quad J_{CD} = 6.8$$

$$J_{PH_A} = 14.5 \quad J_{PH_B} = 4.4 \quad J_{PHC} = 1.8$$

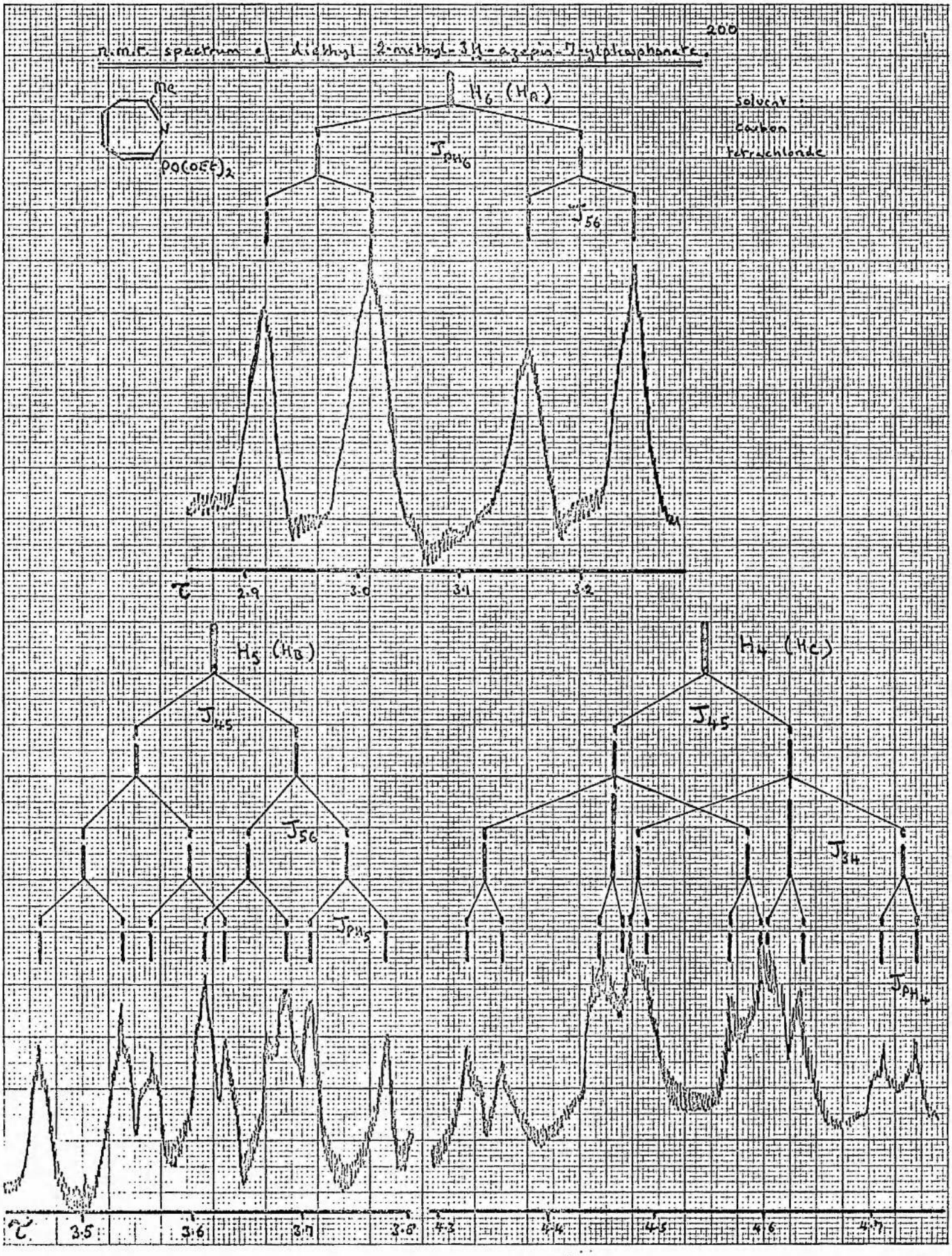
Since there are three large proton coupling constants between the protons H_A, H_B, H_C and H_D, the carbon atoms to which they are attached must be adjacent. The chemical shift of the ring methylene protons is

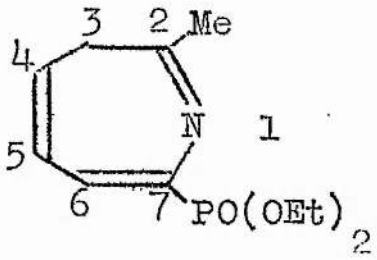
incompatible with their being situated at the 7-position. [The chemical shift of the methylene protons (τ= 7.46) is very similar to that observed for the protons in the 3-position in 2-diethylamino-3H-azepine, (τ= 7.56).[119] If the methylene group were in the 7-position, the chemical shift would be expected to be similar to that of methylene groups in, for example, the diethylamino groups (τ= 6.76).] The coupling constant between P and H_A (J_{PH_A} = 14.5) can only be accommodated by a structure PC=CH (cf. $_P>C=C<_H$ in dimethyl cis-3-pent-2-enylphosphonate J_{PH} = 23.5).[249]

Decoupling experiments confirm that H_C is coupled to the protons H_D, since irradiation at 4.52 causes the doublet at τ= 7.46 to collapse to a broad singlet. Since the proton with the large PH coupling constant must be H_6, the following assignments can be made (τvalues and c/s)

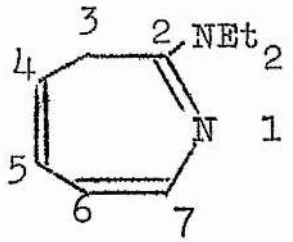
Proton	Assignment	Chemical shift	J_{HH}	J_{PH}
H_A	H_6	2.98	J_{56}=6.0	J_{PH_6}=14.5
H_B	H_5	3.60	J_{45}=8.9	J_{PH_5}=4.4
H_C	H_4	4.52	J_{34}=6.8	J_{PH_4}=1.8
$H_D(2)$	$H_3(2)$	7.46		

n.m.r. spectrum of diethyl 2-methyl-3H-azepin-7-ylphosphonate.





The chemical shifts and proton coupling constants of these protons may be compared with those observed for the corresponding protons in 2-diethylamino-3H-azepine:

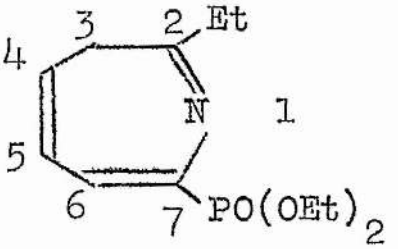


	Assignment	Chemical Shift	J_{HH} c/s
	H_5	3.73	
	H_4	4.98	$J_{56}=5.5$
	H_3	7.56	$J_{45}=8.7$

The compound may, therefore, be formulated as diethyl 2-methyl-3H-azepin-7-ylphosphonate, and a theoretical spectrum, built up for the above coupling constants, may be related to the actual spectrum as shown.

The azepine from the reaction of o-ethylnitrobenzene with triethylphosphite. The n.m.r. spectrum, in carbon tetrachloride, of the product isolated from this experiment is identical in all but two respects with that of the product described above. There is an additional triplet, 3H, τ= 8.70 and the doublet at τ= 7.46 now appears as part of a complex pattern, 4H, centred at

τ= 7.52. These differences are compatible with the substitution of an ethyl group for the ring methyl group in the azepine described above. The product may, therefore, be formulated as diethyl 2-ethyl-3H-azepin-7-ylphosphonate:

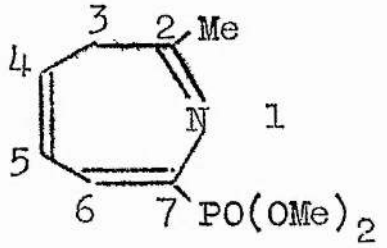


The coupling constants and chemical shifts obtained from this spectrum are described below:

Assignment	Chemical shift	J_{HH}	J_{PH}	c/s
H_6	3.12	J_{56}=6.0	J_{PH_6}=14.3	
H_5	3.65	J_{45}=8.9	J_{PH_5}=4.5	
H_4	4.64	J_{34}=7.0	J_{PH_4}=1.8	
H_3(2)	ca.7.50			

The azepine from the reaction of o-nitrotoluene with trimethyl phosphite. As can be seen from the series of spectra facing p.108, the n.m.r. spectrum, in deuterochloroform, of this azepine is virtually identical with those described already. The spectrum shows a singlet,

3H, τ= 7.80 and a doublet, 6H, τ= 6.23, J = 10 c/s which may be assigned to a ring methyl group and to a methoxy group attached to phosphorus, respectively, in addition to the ring protons.



assignment:	H_6	H_5	H_4	H_3(2)
chemical shift:	3.02	3.55	4.44	7.43

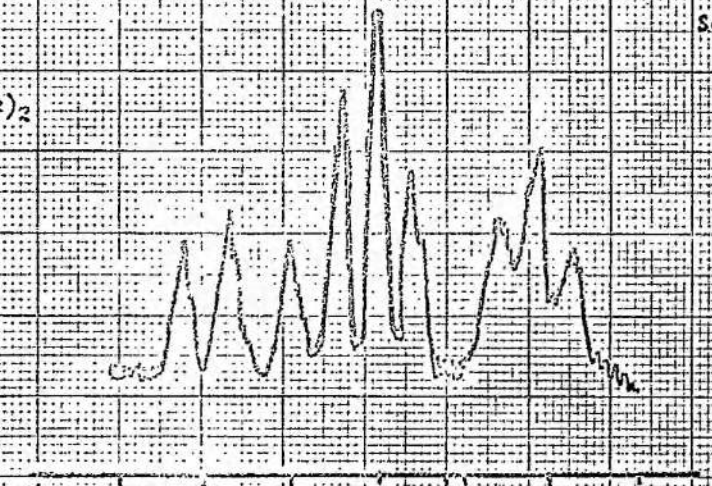
Coupling constants have not been obtained for this compound. It may, however, be formulated as dimethyl 2-methyl-3H-azepin-7-ylphosphonate.

The azepine from the reaction of p-nitrotoluene with trimethyl phosphite. The n.m.r. spectrum, in deuterochloroform, of the azepine isolated from this reaction again exhibits a general similarity to those spectra described already. In particular, the doublet at τ = 7.46 and the quartet at τ= 2.94 remain unchanged. The spectrum also shows a singlet, 3H, τ= 7.90 and a doublet, 6H, τ= 6.25, J = 11 c/s, which may be assigned as before to a ring methyl group and to a methoxy group attached to phosphorus. The ring protons appear as a quartet, 1H, H_A, τ = 2.94; a triplet, 1H, H_B, τ = 3.28;

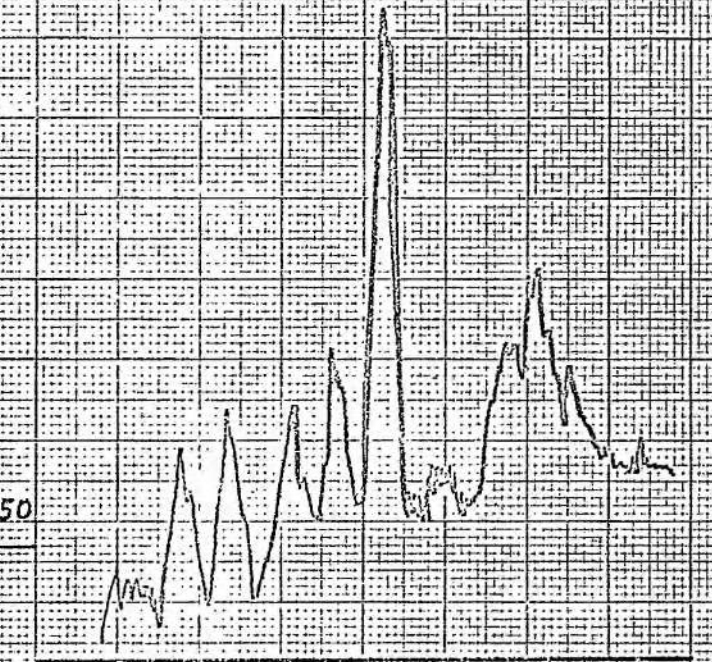
n.m.r. spectrum of dimethyl 4-methyl-3H-azepin-7-ylphosphonate

Solvent : benzene

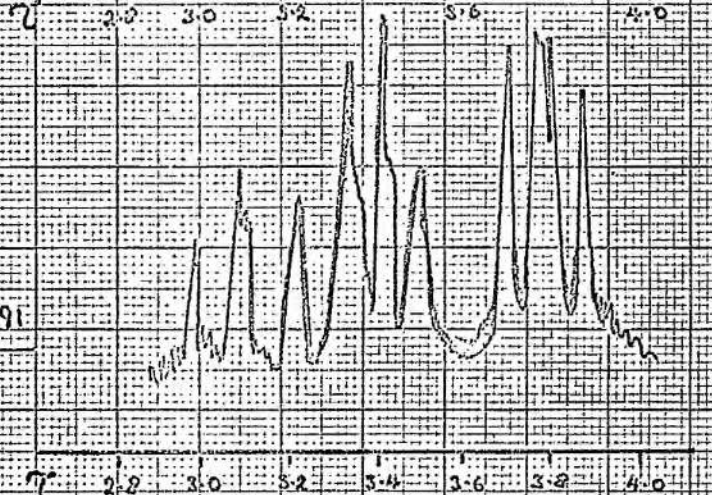
a not irradiated



b irradiated at τ = 7·50



c irradiated at τ = 7·91



a triplet, with further splitting, 1H, H_C, τ= 3.70; and a doublet, 2H, $H_D(2)$, τ= 7.46.

The n.m.r. spectrum of the azepine in benzene shows small solvent shifts, leading to the overlap of the signals from protons H_A and H_B. This does not, however, affect the interpretation of the spectrum. The chemical shifts are now as follows:

proton:	H_A	H_B	H_C	$H_D(2)$	ring methyl
chemical shift:	3.14	3.42	3.80	7.50	7.91

Irradiation at τ= 7.50 (ring methylene) causes the triplet at τ= 3.42 to collapseto a singlet, but has no effect on either of the other two protons H_A and H_C. Irradiation at τ= 7.91 (ring methyl) causes the triplet at τ= 3.80 to sharpen to a doublet of doublets, but again has little effect on the downfield protons H_A and H_B.

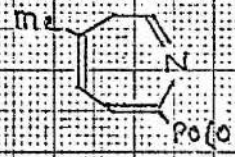
The structure is now fully defined. Proton H_A is coupled to some other nucleus, in addition to the adjacent olefinic proton (J = 6.0 c/s.). This, from the size of the coupling constant (J = 14.0 c/s.) can only be the phosphorus atom. As only one proton shows this large coupling, the carbon bearing the phosphorus atom must be adjacent to the methylene group or to nitrogen:

as, in the first case, however, the methylene group would no longer appear as a doublet, the carbon bearing the phosphorus atom must therefore be adjacent to the nitrogen atom, and $H_A = H_6$, as before.

Irradiation at $\tau = 7.50$ (methylene) affects H_B only, causing the triplet at $\tau = 3.42$ to collapse to a singlet. H_B therefore has no proton neighbours, other than the methylene group, and, as it is not coupled with phosphorus, must be adjacent to the nitrogen atom. The methylene group must also be adjacent to the ring methyl (as the methylene group has only one adjacent proton).

Irradiation at $\tau = 7.91$ causes the triplet at $\tau = 3.80$ to sharpen to a doublet of doublets, but has no effect on any other proton. This confirms that the ring methyl is adjacent to the methylene group or to the phosphorus atom (which would give further coupling) or to the nitrogen atom (already excluded as a possibility) and shows that the one olefinic proton adjacent to the ring methyl is coupled with a second proton and another nucleus, which again can only be phosphorus. The azepine may therefore be formulated as dimethyl 4-methyl-3H-azepin-7-ylphosphonate.

n.m.r. spectrum of dimethyl 4-methyl-3H-azepin-7-ylphosphonate



solvent: benzene

H_6 (H_A)

J_{PH_6}

J_{56}

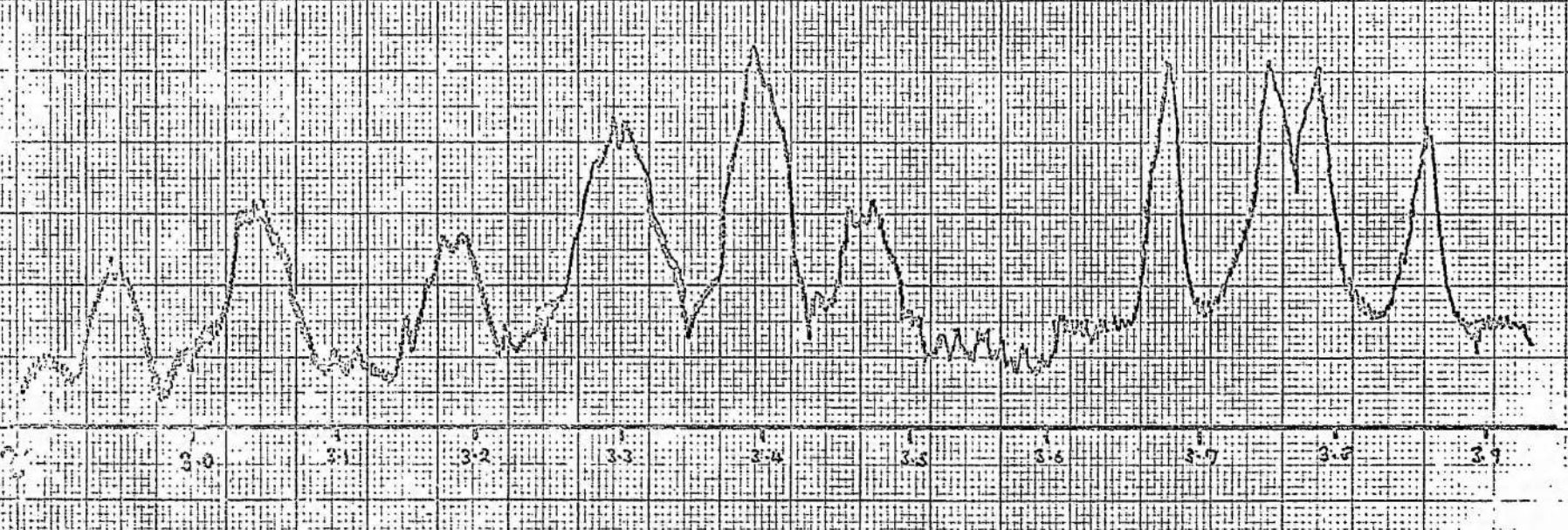
H_2 (H_B)

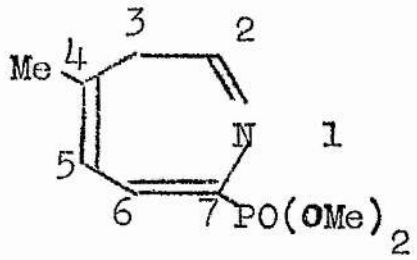
J_{23}

H_5 (H_C)

J_{PH_5}

J_{56}



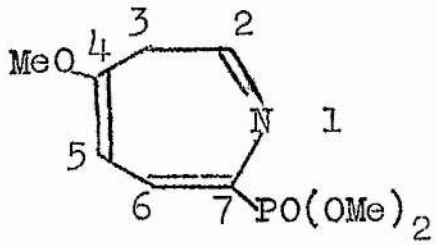


Proton	Assignment	Chemical shift	J_{HH}	J_{PH} (c/s)
H_A	H_6	3.14	J_{56}=6.2	J_{PH_6}=14.0
H_B	H_2	3.42	J_{23}=4.5	J_{PH_5}=4.2
H_C	H_5	3.80		
$H_D(2)$	$H_3(2)$	7.50		

A theoretical spectrum, built up from these coupling constants may be related to the actual spectrum, as shown

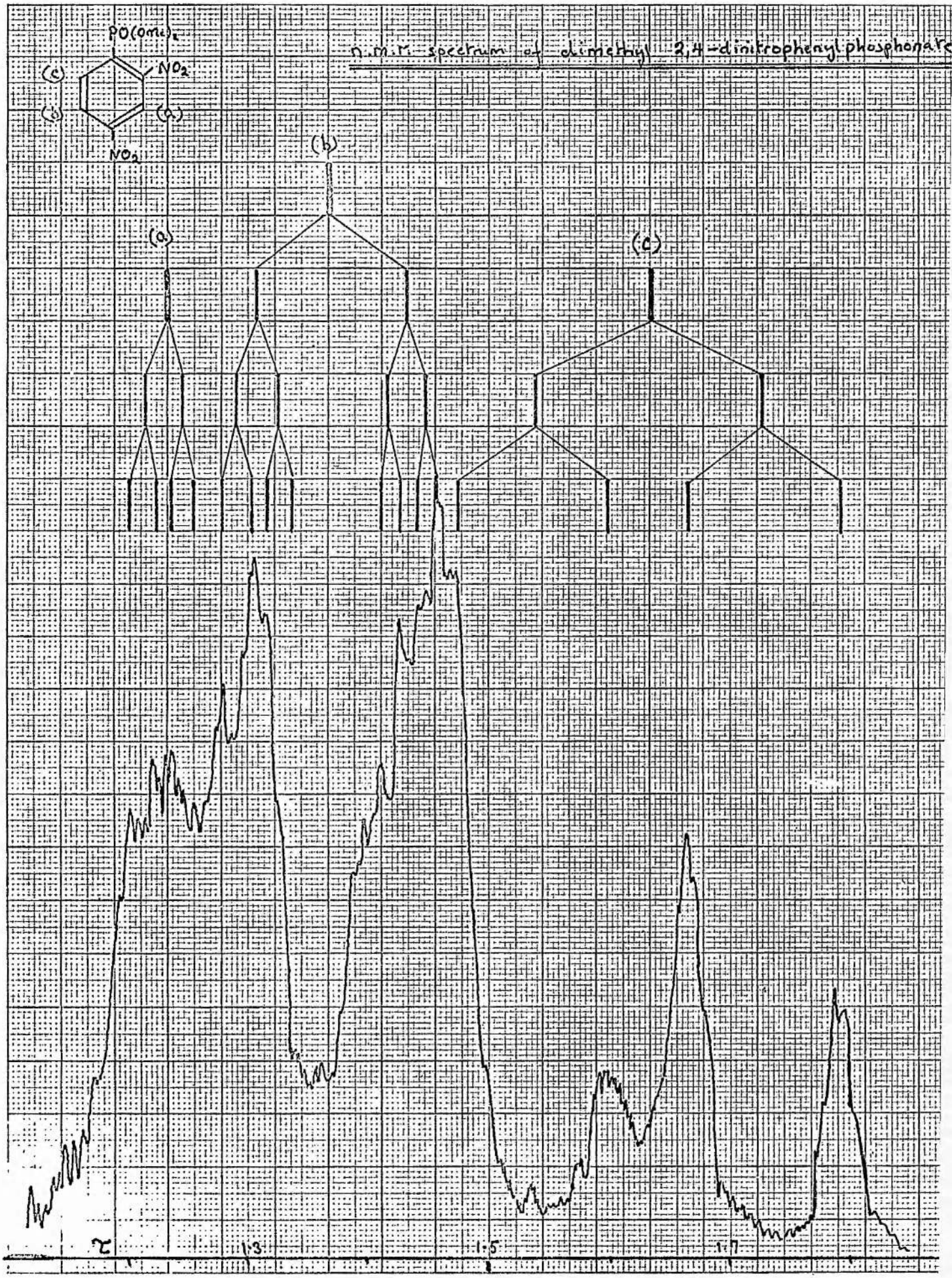
The suspected azepine from the reaction of p-nitroanisole with trimethyl phosphite. The n.m.r. spectrum in deuterochloroform, of this suspected azepine, shows a singlet, τ= 6.32, with a doublet, τ = 6.24, J = 11 c/s., superimposed upon it, total ca. 9H. The ring protons appear as a quartet, 1H, H_A, τ= 2.92; a triplet, 1H, H_B, τ= 3.25; a quartet, with further splitting, 1H, H_C, τ= 4.37; and a doublet, 2H, $H_D(2)$, τ= 7.33. Additional peaks (doublet, τ= 6.86, J = 9 c/s, others in aromatic region) suggest that this azepine has not yet been obtained in analytical purity.

However, a scale expansion of the region from τ= 2.5 to 5.0 gives the following, tentative, values for chemical shifts and coupling constants: no decoupling experiments have, as yet, been undertaken on this system.



Proton	Assignment	Chemical shift	J_{HH}	J_{PH} (c/s)
H_A	H_6	2.92	J_{56}=7.25	J_{PH_6}=14.0
H_B	H_2	3.25	J_{23}=5.0	J_{PH_5}=4.1
H_C	H_5	4.37		
$H_D(2)$	$H_3(2)$	7.33		

(ii) Other structural problems in the light of n.m.r. spectral evidence: confirmation of the structure of 2,4-dinitrophenylphosphonates. Trialkyl phosphites react with 1,2,4-trinitrobenzene to give, by nucleophilic displacement of a nitro-group, the corresponding 2,4-dinitrophenylphosphonates. The formulation of these compounds as the 2,4- rather than the 2,5- or 3,4-dinitrophenylphosphonates depends upon an analysis of the aromatic region of the n.m.r. spectra of these


PO(OMe)2
NO2
NO2
(c)
(b)
(a)
n.m.r. spectrum of dimethyl 2,4-dinitrophenyl phosphonate
(b)
(a)
(c)
τ
1·3
1·5
1·7

compounds. The spectra have been described earlier (p. 72-74). With only three protons present, the aromatic region of these spectra might be expected to be relatively simple: the phosphorus atom is however coupled with both o- and m-protons. The spectrum, and the interpretation thereof, for dimethyl 2,4-dinitrophenylphosphonate is as shown opposite. Similar spectra have been obtained for diethyl and di-isopropyl 2,4-dinitrophenylphosphonate. The coupling constants (c/s) and chemical shifts derived from these spectra are listed below.

	J_{PH_o}	J_{PH_m}	J_{PH_p}	J_{HH_o}	J_{HH_m}	J_{HH_p}
dimethyl	12.5	2.5	-	8.2	1.5	ca. 0
diethyl	12.4	2.2	-	8.4	1.0	ca. 0
di-isopropyl	9.0	2.7	-	8.5	1.5	ca. 0

These may be compared with corresponding values for a variety of phosphines and phosphine oxides,[213,214] where J_{PH_o} =7.9-11.5; J_{PH_m} =2.1-3.4 and J_{HH_o} =8.0-8.9.

Confirmation of the structures of authentic samples of the phosphorus-containing compounds described in TABLES 1-4 (p. 49-51). Authentic samples of a number of dialkyl arylphosphonates, trialkyl N-arylphosphorimidates, dialkyl N-alkyl-N-arylphosphoramidates and dialkyl N-arylphosphoramidates have been prepared by

established methods, as described. Identification of these is based upon their means of preparation, upon their elemental analysis, and upon the relevant spectral data.

The n.m.r. spectra, in deuterochloroform, show the presence of alkyl substituents in the aromatic system, and of alkoxy groups attached to phosphorus. Other than in the spectra of the dialkyl arylphosphonates, the aromatic region appears as a singlet or as an unresolved multiplet centred between $\tau = 2.6$ and $\tau = 3.4$. In contrast, the dialkyl arylphosphonates, in particular when the alkyl substituent on the benzene ring is in the p-position, show cleanly resolved eight-line A_2B_2X aromatic resonance spectra. These spectra have been fully analysed by Obrycki and Griffin.[183]

For the methyl esters, the P-O-CH_3 doublet appears in the range $\tau = 6.2$ to $\tau = 6.35$, with J_{PH} = 10-12 c/s. For the ethyl esters, typical P-O-CH_2-CH_3 resonances are observed: triplets, τ = 8.65-8.75, $J_{HH} \cong$ 7-8 c/s and quintets (i.e. doublets of quartets), τ = 5.85-5.90, $J_{HH} \cong J_{PH}$ = 7-8 c/s, representing the methyl and the methylene groups respectively.

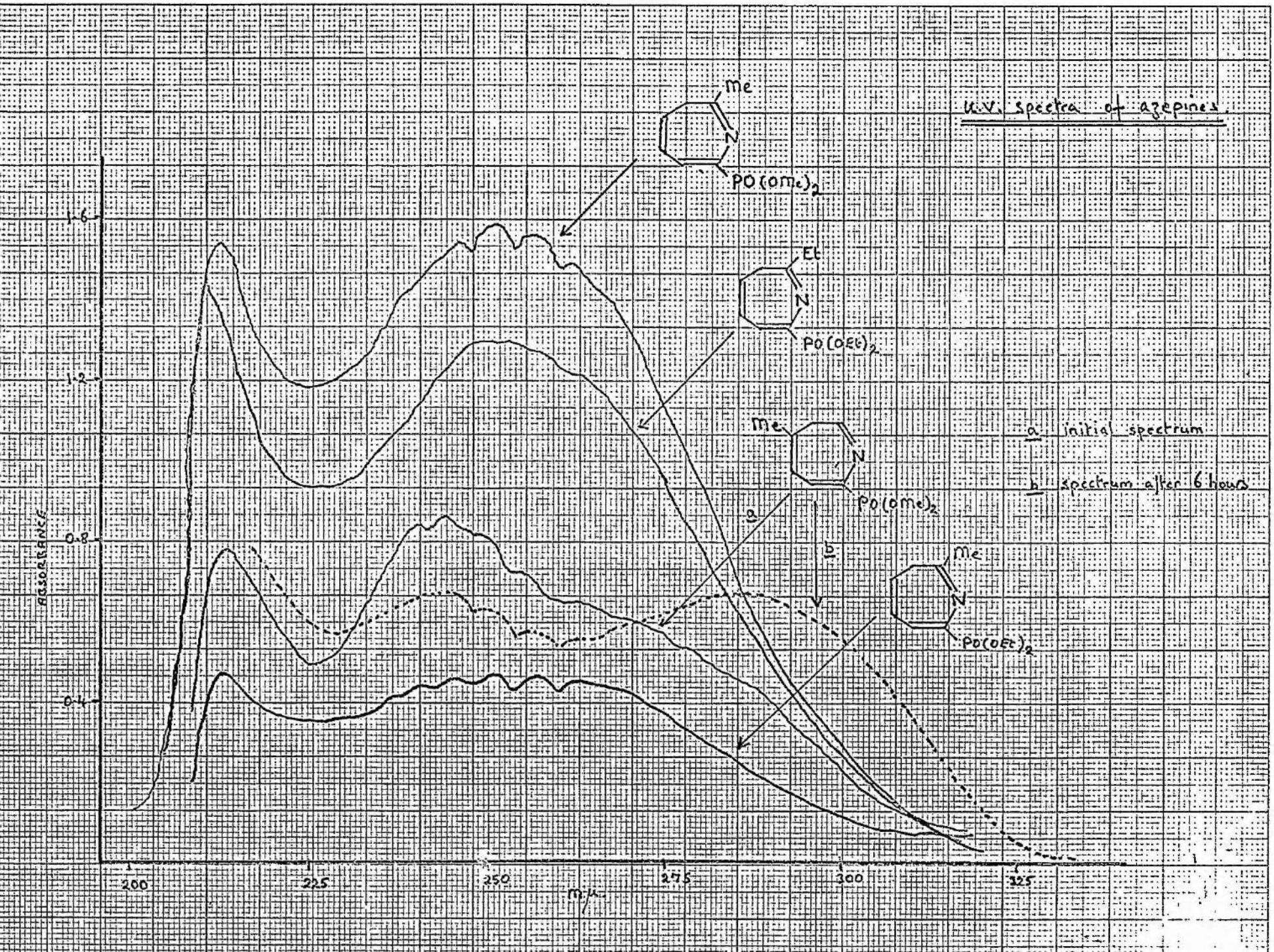
The N-methyl group, in the dimethyl N-methyl-N-arylphosphoramidates, appears as a doublet, τ = 6.8-

7.1, J=7-8 c/s. The corresponding N-ethyl group appears as two overlapping quartets, not always cleanly resolved, τ= 6.4-6.8, J_{HH}=6-8 c/s and as a, presumed, triplet, τ= 8.6-8.8, which is always overlapped by the triplet resulting from the methyl resonance of the ethoxy group attached to the phosphorus atom.

The single proton attached to nitrogen in dialkyl N-arylphosphoramidates may show as a broad singlet in the range τ= 4.5-5.5. However, in different environments, this range may be exceeded, and if the peak becomes too broad, it may be impossible to identify it. However, i.r. spectroscopy clearly shows the presence of such N-H groups. Chemical shifts for other nuclear substituents (alkyl and alkoxy) fall within normally accepted ranges for these groups.

Satisfactory integrated intensities have been obtained in every case.

The quantitative analysis of mixtures of the phosphorimidates and phosphoramidates, described above, depends on a comparison of the integrated intensities of the aromatic, P-OCH_2- or P-OCH_3, N-CH_2- or N-CH_3, and ArCH_2- or ArCH_3, regions. It will be apparent that, in order to achieve this, the spectra should show as little overlapping of the different resonances as possible.


U.V. Spectra of azepines.
Me
N
PO(OMe)2
Et
N
PO(OEt)2
Me
N
PO(OMe)2
Me
N
PO(OEt)2
a initial spectrum
b spectrum after 6 hours
a
b
ABSORBANCE
1·6
1·2
0·8
0·4
200
225
250
275
300
325
mμ

Thus the reaction of trimethyl phosphite with o-, m- and p-nitrotoluene leads to a mixture of products which are most susceptible to analysis in this way.

It may be possible, in some cases, to distinguish the phosphorimidates from the phosphoramidates by the chemical shift of the aromatic proton resonance, this being generally in the range τ= 3.10-3.25, for the centre of the multiplet, in the former case, and in the range τ= 2.75-2.85, in the latter.

(b) Ultra-violet Absorption Spectra. The u.v. spectra, in methanol, of four of the azepines isolated, have been recorded (λ_{max}: ca. 255 mμ). A qualitative comparison of their spectra may be made, as shown. The concentrations of the solutions are not the same and the maxima do not, therefore, indicate the relative extinction coefficients.

The spectra show a considerable similarity, with little variation with the nature or position of the alkyl substituent. This is further evidence for the formation of the same 3H-azepine ring system in each case. It may also be seen, however, that the spectrum of dimethyl 4-methyl-3H-azepin-7-ylphosphonate shows a noticeable change after the solution in methanol has been allowed to stand for a number of hours. This is not so for any of the other azepines investigated in

this way. This does confirm analytical and visual evidence that this particular azepine is less stable than the others discussed here, although the products of this decomposition or rearrangement have not been studied further.

(c) Infra-red Spectra. The i.r. spectra of a number of phosphorus-containing compounds have been recorded as described. The characteristic absorptions of these compounds ($\nu_{P=O}$=1200-1260; ν_{POC}=1010-1040; ν_{POEt}= 1155-1165 cm.$^{-1}$; et cet.) in general fall within the ranges defined by Thomas and Chittenden.[209-212]

The close agreement of the values of the P=O absorption frequencies with those calculated by the method of Thomas and Chittenden[209] is of particular interest. It was shown, by them, that there is a linear relationship between the phosphoryl frequency and the sum of the 'phosphorus inductive constants (π)', these constants being empirical values, related to the Pauling electronegativity constants for the different groups, such that:

$$\nu_{P=O} = 930 + 40 \sum \pi$$

This relationship does not hold, in general, for phosphine oxides and phosphoramidates, owing possibly,

INFRA-RED SPECTRAL DATA (i)

(cm^{-1}

$$\nu_{P=O} = 930 + 40 \sum\pi$$

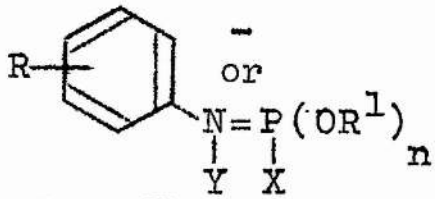
Compound	$\sum\pi$	$\nu_{P=O}$(calc.)	$\nu_{P=O}$(obs
Ethyl diphenylphosphinate	7.65	1236	1230
Dimethyl o-nitrophenylphosphonate	8.2	1258	1250
Diethyl o-nitrophenylphosphonate	8.1	1254	1247
Di-isopropyl o-nitrophenylphosphonate	7.9	1246	1248
Ethyl methyl-o-nitrophenylphosphinate	7.35	1224	1225
Diphenyl-o-nitrophenylphosphine oxide	7.2	1218	1195
Dimethyl 2,4-dinitrophenylphosphonate	8.2	1258	1260
Diethyl 2,4-dinitrophenylphosphonate	8.1	1254	1260
Di-isopropyl 2,4-dinitrophenylphosphonate	7.9	1246	1255
Dimethyl N-arylphosphoramidates	7.8	1242	1225-125
Dimethyl N-methyl-N-arylphosphoramidates	8.0	1250	1245-126
Diethyl N-arylphosphoramidates	7.7	1238	1225-125
Diethyl N-ethyl-N-arylphosphoramidates	7.9	1246	1245-126

to hydrogen-bonding or steric effects.

The spectra now described show that the P=O absorption frequency of diphenyl-o-nitrophenylphosphine oxide (1195 cm.$^{-1}$) does indeed differ markedly from that suggested by the above theory (1218 cm.$^{-1}$). The values obtained from the various phosphoramidates are rather closer to those required (see Spectral Data (i), opposite).

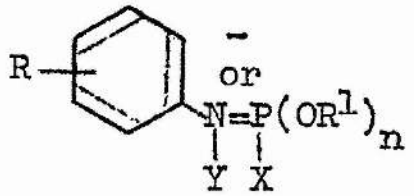
All the other values are in good agreement ($\pm$9 cm.$^{-1}$) with the values suggested by the above theory, and well within the limits ($\pm$12 cm^{-1}) described by Thomas and Chittenden. This is not, in fact, the expected result, for, if steric effects and possible electronic interactions are important in perturbing the P=O frequency in aromatic phosphine oxides, then the same effects should be noticeable with a bulky ortho-substituent, such as the nitro-group. This is not apparently the case, however, for despite the presence of the o-nitro-group in each of the phosphonates described, the observed P=O frequencies, as has been shown, remain close to those values predicted by the theory. It may be, in turn, that some perturbing factors other than steric effects are important in causing the anomalous absorptions of triarylphosphine oxides.

INFRA-RED SPECTRAL DATA (ii)



R	R^1	n	bond	X	Y	$\nu_{P=N}$	ν_{P-N} ?	$\nu_{P=O}$	ν_{N-H}
o-Me	Me	3	≡			1360 1375			
"	"	2	–	O	Me		930	1260	
"	"	2	–	O	H		995	1245	3200
"	Et	2	–	O	H		940	1240	3190
m-Me	Me	3	≡			1365			
"	"	2	–	O	Me		940	1255	
"	"	2	–	O	H		980	1235	3180
"	Et	3	≡			1360 1380			
"	"	2	–	O	Et		?	1265	
"	"	2	–	O	H		?	1235	3180
p-Me	Me	3	≡			1380			
"	"	2	–	O	Me		920	1265	
"	"	2	–	O	H		995	1230	3170
"	Et	3	≡			1360 1380			
"	"	2	–	O	Et		910	1260	
"	"	2	–	O	H		?	1230	3165

INFRA-RED SPECTRAL DATA (iii)



R	R^1	n	bond	X	Y	$\nu_{P=N}$	ν_{P-N} ?	$\nu_{P=O}$	ν_{N-H}
o-OMe	Me	3	=			1380			
"	"	2	-	O	Me		965	1250	
"	"	2	-	O	H		970	1250	3210
"	Et	3	=			1385			
"	"	2	-	O	Et		?	1260	
"	"	2	-	O	H		?	1250	3220
m-OMe	Me	3	=			1370			
"	"	2	-	O	Me		955	1260	
"	"	2	-	O	H		985	1235	3180
"	Et	3	=			1360 1375			
"	"	2	-	O	Et		780?	1250	
"	"	2	-	O	H		775?	1250	3170
p-OMe	Me	3	=			1365			
"	"	2	-	O	Me		920	1245	
"	"	2	-	O	H		980	1225	3170
"	Et	3	=			1360 1380			
"	"	2	-	O	Et		?	1245	
"	"	2	-	O	H		?	1225	3180

The values for $\nu_{P=N}$ for the trialkyl N-arylphosphorimidates, for $\nu_{P=O}$ and ν_{P-N} for the dialkyl N-alkyl-N-arylphosphoramidates, and for $\nu_{P=O}$, ν_{P-N} and ν_{N-H} for the dialkyl N-arylphosphoramidates are shown in Spectral Data (ii) and (iii). The values for ν_{P-N} are, of course tentative, as this correlation has not been clearly established, as yet. While the absorption in the region 920-965 cm.$^{-1}$ for dialkyl N-alkyl-N-arylphosphoramidates, and in the region 970-995 cm.$^{-1}$ for the dialkyl N-arylphosphoramidates, is quite consistent for the methyl esters, the corresponding absorptions for the ethyl esters are far less obvious. This correlation, as suggested by Thomas and Chittenden[212], must therefore remain in question.

The i.r. spectra of the dialkyl arylphosphonates, which all show $\nu_{P=O}$=1250±5 cm.$^{-1}$, in accord with the theory described earlier, have been fully described by Obrycki and Griffin.[183]

Finally, the i.r. spectra of diethyl 2-methyl- and 2-ethyl-3H-azepin-7-ylphosphonate have been described in full, elsewhere.[200] The i.r. spectra for three further azepines may now be described: see Spectral Data (iv) on following page.

SPECTRAL DATA (iv)

Dimethyl 2-methyl-3H-azepin-7-ylphosphonate:

3000 (w.), 2960 (s.), 2850 (m.), 1610 (s.), 1520 (w.), 1430 (m.), 1395 (m.), 1370 (m.), 1330 (w.), 1280 (m.), 1255 (s.), 1180 (m.), 1170 (m.), 1115 (s.), 1065 (s.), 1030 (s.), 965 (w.), 905 (w.), 860 (w.), 830 (s.), 800 (w.), 780 (s.), 750 (s.), 655 (w.).

Dimethyl 4-methyl-3H-azepin-7-ylphosphonate:

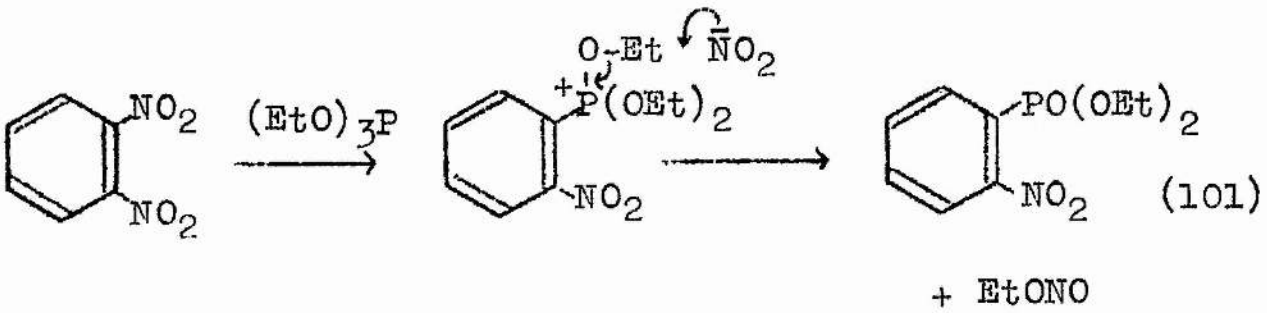
3000 (w.), 2950 (s.), 2850 (m.), 1610 (m.), 1590 (m.), 1525 (m.), 1450 (s.), 1375 (m.), 1345 (w.), 1255 (s.), 1185 (s.), 1115 (w.), 1100 (s.), 1030 (s.), 950 (w.), 920 (w.), 905 (w.), 875 (w.), 830 (s.), 810 (w.), 800 (m.), 775 (s.), 680 (w.), 650 (m.).

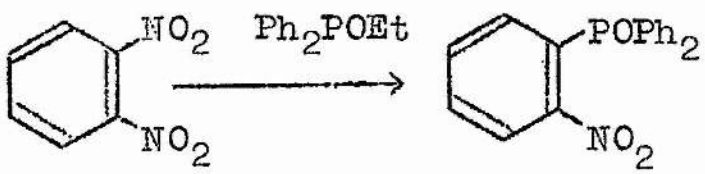
Dimethyl 4-methoxy-3H-azepin-7-ylphosphonate:

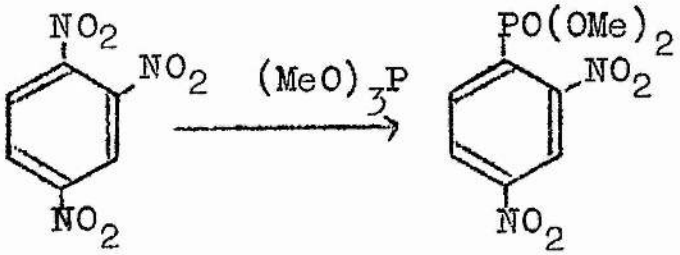
3000 (m.), 2950 (s.), 2850 (m.), 1650 (m.), 1600 (s.), 1520 (s.), 1460 (m.), 1440 (m.), 1420 (m.), 1375 (m.), 1360 (m.), 1290 (s.), 1250 (s.), 1200 (m.), 1170 (s.), 1100 (s.), 1035 (s.), 950 (w.), 915 (w.), 900 (w.), 875 (w.), 830 (s.), 780 (s.), 680 (m.).

s.= strong m.= medium w.= weak.

DISCUSSION


NO2
NO2
(EtO)3P
O-Et
NO2
+P(OEt)2
NO2
PO(OEt)2
NO2
(101)
+ EtONO


NO2
NO2
Ph2POEt
POPh2
NO2


NO2
NO2
NO2
(MeO)3P
PO(OMe)2
NO2
NO2

SCHEME 20

The Reactions of Tervalent Phosphorus Reagents with Aromatic Nitro-Compounds.

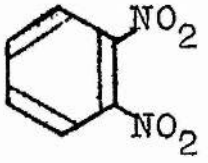
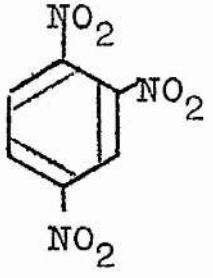
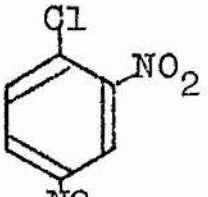
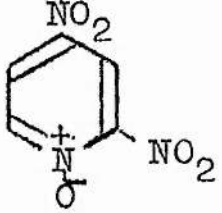
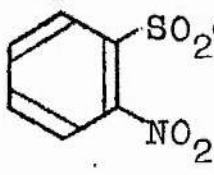
It is apparent from the experimental work described in previous chapters that the reaction of tervalent phosphorus reagents with o-dinitrobenzene and related compounds differs markedly from the corresponding reactions with o-alkylnitroso- and alkylnitrobenzenes. The two series of experiments will therefore be discussed separately, both in terms of their indication of the possibilities for synthesis, and in terms of their contribution to the understanding of the mechanism of the reactions concerned.

1. Reaction of o-Dinitrobenzene and Related Compounds with Tervalent Phosphorus Reagents.

(a) Preparative aspects of this reaction. It has now been shown that phosphites, phosphonites and phosphinites react readily with o-dinitrobenzene and with 1,2,4-trinitrobenzene, and to a much smaller extent with some other aromatic nitro-compounds, to give the corresponding o-nitrophenyl- and 2,4-dinitrophenylphosphonates, phosphinates and phosphine oxides, in high yields. A mechanism involving aromatic nucleophilic substitution

TABLE 5

Reactions showing aromatic nucleophilic substitution by tervalent phosphorus reagents.

Nitro-Compound	Phosphorus Reagent	Products Formed
	$(MeO)_3P$	dimethyl o-nitrophenylphosphonate (67%)
	$(EtO)_3P$	diethyl o-nitrophenylphosphonate (50-78%) ethyl nitrite (25-48%)
	$(Pr^iO)_3P$	di-isopropyl o-nitrophenyl-phosphonate (54%)
	$(EtO)_2PMe$	ethyl methyl-o-nitrophenyl-phosphinate (77%)
	$(EtO)PPh_2$	diphenyl-o-nitrophenylphosphine oxide (65%)
	$(EtO)_2PO^-Na^+$	diethyl o-nitrophenylphosphonate (9.8%)
	$(MeO)_3P$	dimethyl 2,4-dinitrophenyl-phosphonate (73%)
	$(EtO)_3P$	diethyl 2,4-dinitrophenyl-phosphonate (54%) 2,4-dinitrophenol (5.8%)
	$(Pr^iO)_3P$	di-isopropyl 2,4-dinitrophenyl-phosphonate (48%)
	$(EtO)_3P$	diethyl 2,4-dinitrophenyl-phosphonate (11.2%)
	$(EtO)_3P$	diethyl 2-pyridylphosphonate (35%)
	$(EtO)_3P$	diethyl o-nitrophenylphosphonate (8%)

by the phosphorus moiety is proposed (Scheme 20). Not only is this a novel reaction of tervalent phosphorus reagents, there being few, if any, other established examples of heterolytic aromatic substitution by phosphorus compounds, but it is also a convenient route to compounds previously difficult to prepare.

A summary of those experiments which show, or appear to show*, aromatic nucleophilic substitution, is given in TABLE 5. In a number of experiments, this expected reaction fails to take place, giving instead deoxygenation or reduction products, similar to those found in reactions between tervalent phosphorus reagents and unactivated nitrobenzenes, or leading to the recovery of starting materials, or giving black intractable tars after an exothermic reaction. The results of these experiments are described in TABLE 6, and the possible reasons for these limitations to the reaction as a general method of synthesis will be discussed in the light of the postulated mechanism for the reaction.

The difficulties inherent in the synthesis of the

*Alternative mechanisms will be discussed in due course. Aromatic nucleophilic substitution is however, at present, the most useful hypothesis for the interpretation of these results.

TABLE 6

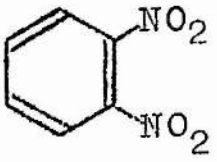
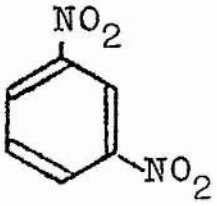
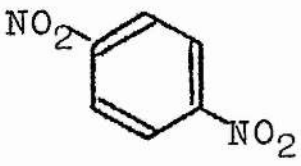
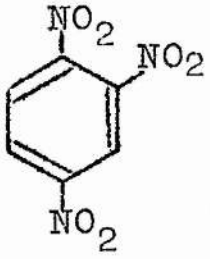
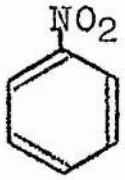
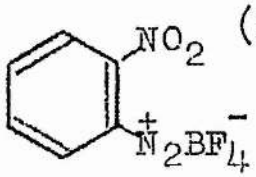
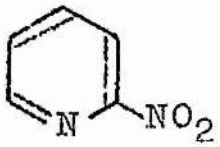
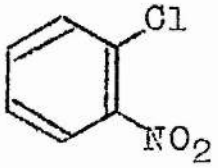
Nitro-Compound	Phosphorus Reagent	Products formed
	Bu^n_3P	unchanged nitro-compound
	Ph_3P	triphenylphosphine oxide, tars
		nitric oxide (?)
	$(EtO)_3P$	tars formed
	$(MeO)_3P$	no reaction in solution
	$(EtO)_3P$	violent reaction in absence of solvent, tars formed
		no reaction in solution
	$(Pr^iO)_3P$	no reaction in solution
	$(EtO)_2PMe$	p-nitrophenetole (3.2%),
		N-ethyl-p-nitroaniline (1.9%)
		p-nitroaniline (8.6%)
	$(EtO)PPh_2$	unchanged nitro-compound (42%)
	$(EtO)PPh_2$	violent reaction, nitrous fumes, tars formed
	Ph_3P	triphenylphosphine oxide (45%)

TABLE 6 (ii)

Nitro-Compound	Phosphorus Reagent	Products formed
	$(EtO)_3P$	tars
	$(EtO)_3P$	2-nitrobiphenyl (12-14%), o-nitroaniline (11%), N-ethyl-o-nitroaniline (6%) } solution in benzene
	$(EtO)_3P$	no reaction in solution tars formed in absence of solvent
	$(EtO)_3P$	no reaction in solution, tars found in absence of solvent
	$(EtO)_3P$	unchanged nitro-compound (42%) in solution tars, ethyl chloride (53%) in absence of solvent

products of this reaction, by alternative routes, may be illustrated by the failure of previous attempts to prepare diethyl o-nitrophenylphosphonate (101). Kosolapoff,[215,216] in 1948-49, nitrated diethyl phenylphosphonate, but was unable to separate the resulting mixture of o-, m-, and p-isomers of diethyl nitrophenylphosphonate or of the corresponding acid. Doak, Freedman and Jaffe developed a satisfactory method for the preparation of arylphosphonic acids from the corresponding benzenediazonium fluoroborate and phosphorus trichloride in the presence of copper salts, which failed in the case of o-nitrobenzenediazonium fluoroborate.[187] They were later able to separate the o-, m-, and p-isomers of nitrophenylphosphonic acid, described above, by the fractional crystallisation of their magnesium salts.[186] The diethyl ester was not, however, prepared from o-nitrophenylphosphonic acid. Other investigations, of nitrogen mustards containing the phosphonate group[217] and of phosphorus esters prepared from the acids by the action of phosphorus pentachloride and the appropriate alcohol,[218] made no mention of the o-nitro-isomer.

More recently, Obrycki and Griffin,[183] and Tavs and Korte[219] reported elegant syntheses of a number of

dialkyl arylphosphonates from the corresponding substituted iodo- or bromobenzenes and the appropriate trialkyl phosphite in the presence of ultra-violet light or of copper, respectively. Once again there was a conspicuous failure of these methods in the case of halo-nitro-compounds, the reaction in such cases leading to the recovery of unchanged starting material or to the production of intractable tars.[183]

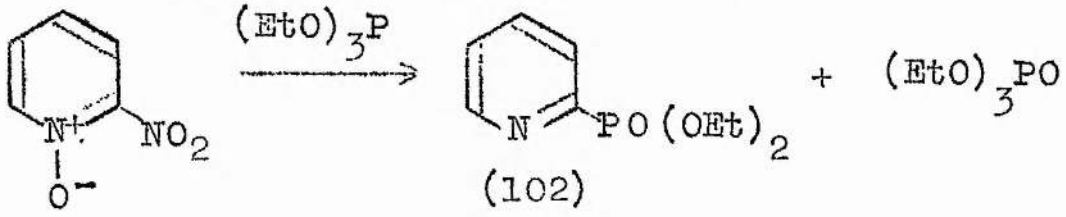
It has now been shown that these dialkyl o-nitrophenylphosphonates are readily available in high yields and, if necessary, on a large scale. A similar situation exists in the case of the other phosphinates and phosphine oxides formed by the use of different tervalent phosphorus reagents. Further syntheses from these materials are of course possible, and investigations have been carried out in this Department[220,221] on the various derivatives produced by reduction of the remaining nitro-group, and by diazotisation under different conditions of the resulting amino-compound. Hydrolysis of the esters by heating under reflux with concentrated hydrochloric acid gives quantitative yields of the free acids.

When o-dinitrobenzene is replaced by 1,2,4-trinitrobenzene, the rate of the reaction with tervalent

phosphorus reagents increases rapidly and may, in the case of ethyl diphenylphosphinite, for example, become difficult to control. Provided, however, that excessive charring of products does not take place, a similar range of products may be isolated.

The halogen in chloro-2,4-dinitrobenzene is sufficiently activated for displacement by triethyl phosphite to occur, as above. This is not so, however, in the reaction of o-chloronitrobenzene. Although, under extreme conditions, the halogen is displaced, as shown by the formation of ethyl chloride, there is no evidence for the formation of diethyl o-nitrophenylphosphonate.

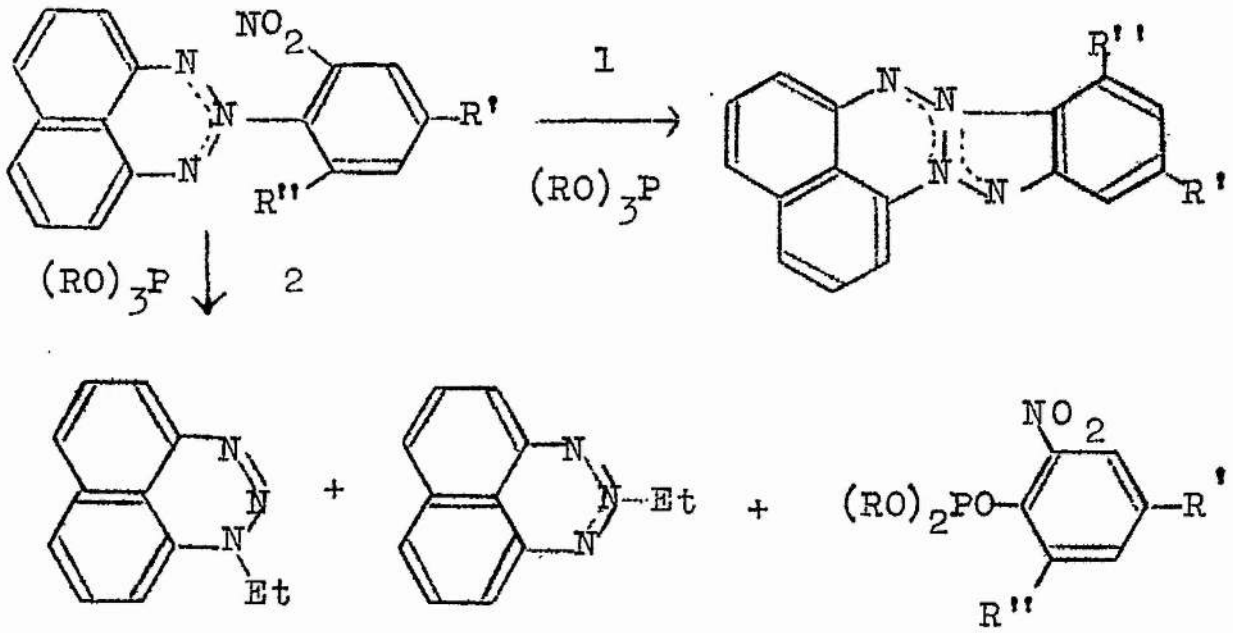
An interesting extension of the reaction to a heterocyclic system involves the reaction of 2-nitropyridine-N-oxide with triethyl phosphite, the main product being 2-pyridylphosphonate (102):



(102)

The difficulty of preparing the starting material precluded any further study of this reaction.

Following the publication of a brief report of this work,[232] two communications have appeared which

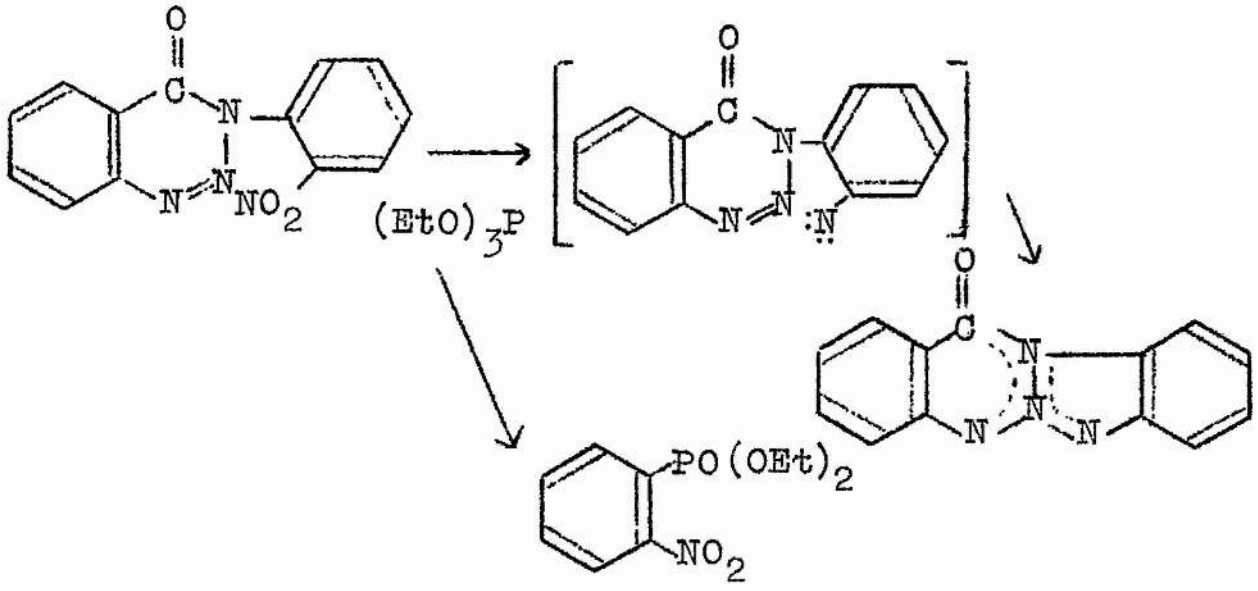


(a) $R' = R'' = H$

(b) $R' = NO_2$, $R'' = H$

(c) $R'' = NO_2$, $R' = H$

SCHEME 21



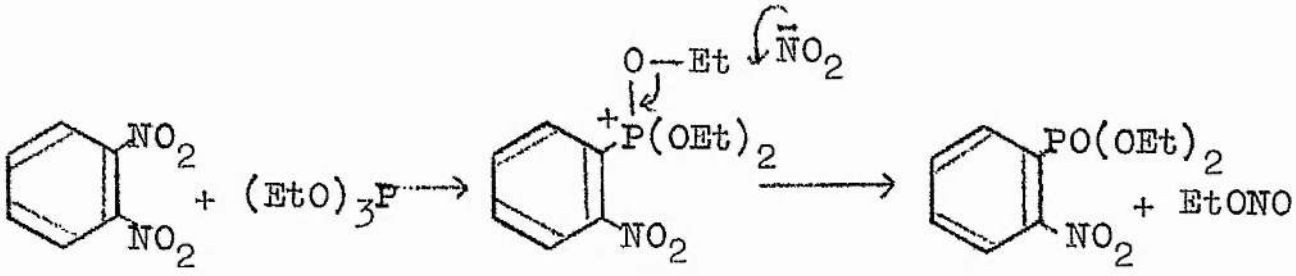
SCHEME 22

describe apparently similar reactions in rather more complex cases. Sieper[223] isolated diethyl o-nitrophenylphosphonate (15%) and two isomeric ethylnaptho-triazines as by-products in the preparation of a new tetra-azapentalene, from the reaction of 2H-2-(2-nitrophenyl)-naphtho[1-8-de]-1,2,3-triazine with triethyl phosphite (Scheme 21). He also found that the substitution reaction was favoured when the 2,4- and 2,6-dinitro-compounds were used in place of the o-nitro-compound. However, the lengthy process of separation by partition of the reaction products in a hexane/methanol/water solvent system, followed eventually by preparative-scale g.l.c., does not really suggest this as a convenient method of synthesis of diethyl o-nitrophenylphosphonate.[223] o-Dinitrobenzene is also more readily available as a starting material for this reaction.

Diethyl o-nitrophenylphosphonate was also isolated in low yield from the preparation of 13-oxobenzotriazolo[2,1-b]benzo[1,2-e]triazine by reaction of 3,4-dihydro-4-oxo-1,2,3-benzotriazine and triethyl phosphite (Scheme 22).[224] In both this case, and that described previously, it is reasonable to suppose that the bulky triazine residues acted as leaving groups, in the same

manner as the replaced nitro-group in o-dinitrobenzene.

(b) Mechanism of this reaction. The reaction of tervalent phosphorus reagents with o-dinitrobenzene appears to involve direct aromatic nucleophilic substitution by the phosphorus reagent with elimination of the nitro-group as ethyl nitrite:



If aromatic nucleophilic substitution is involved, it would be expected that the ease of reaction would vary considerably with the activating effect of the other substituents, and with the mobility of the leaving group, as well as with the nucleophilicity and structural features of the phosphorus reagent. These different factors will be examined in turn here, firstly for aromatic nucleophilic substitution in general, and secondly in relation to the specific experiments carried out in the course of this study.

(i) Mobility of different leaving groups in aromatic nucleophilic substitution. While the importance of electrophilic aromatic substitution has been recognised for some considerable time, the study of aromatic

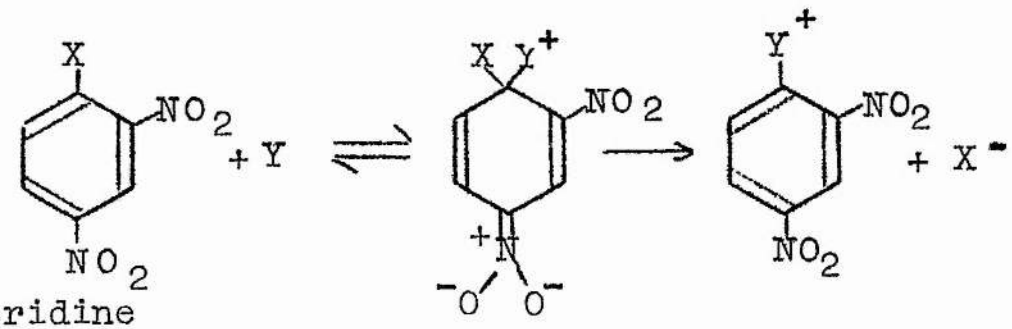
nucleophilic substitution has been undertaken relatively recently. The subject has been reviewed by Bunnett[225,226] in 1951, and again in 1958. In contrast to electrophilic aromatic substitution, it should be noted firstly, that hydrogen itself is rarely replaced, the replaceable groups ordinarily being halogen atoms or other groups capable of reasonable stability as anions; secondly, that it is usually difficult to induce an aromatic nucleophilic substitution to occur, unless there is, in addition to the replaceable group, some activating structure, such as a substituent group (e.g. nitro-group), a heterocyclic nitrogen atom, or some other structural feature capable of withdrawing electrons from the aromatic system; thirdly, that since commonly available compounds seldom possess more than one group replaceable by nucleophilic substitution, it is not meaningful to discuss the "directing powers" of substituents. If the group in question is sufficiently activated, it will be replaced by an appropriate reagent, but if it is not sufficiently activated, no reaction will occur, by this route at least.

Interest in recent years has centred upon the relative ease of displacement of different substituents from aromatic systems, and upon the nature of the

transition state i.e. as to whether the reactions are, in general, unimolecular S_N1-type, or one- or two-stage bimolecular S_N2-type reactions via an intermediate complex. A third possibility, that of the elimination-addition (benzyne) mechanism, does not appear to be relevant here. The unimolecular reaction mechanism has been proposed by Chapman et al.,[227] but it is well-established only for the thermal decomposition of diazonium cations in aqueous solution,[226,228] and this too has been shown to be more complicated than was originally supposed.[229] The choice, in bimolecular displacements, between synchronous, one-stage processes, as in substitution at a saturated carbon atom,[230] and two-stage processes involving a complex tetrahedral intermediate has again been discussed at length. Considerable kinetic evidence consistent with this latter process has however been accumulated by Bunnett,[226,231] Johnson,[232] Pietra,[233] and others.[234] The isolable complexes studied by Meisenheimer[235] are analogous to these intermediates. On the other hand, the one-stage synchronous mechanism has been proposed by Parker and his co-workers[236] to explain the relative ease of displacement of different groups from substituted aromatic compounds (TABLE 9).

However, whatever the mechanism, the kinetic evidence from a variety of experiments is sufficiently consistent to give an "order of replaceability" of

TABLE 7



Y = piperidine

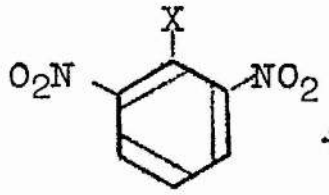
X =	F	NO_2	p-tosyl	SOPh	Br	Cl	SO_2Ph	I
rel. rate ≈	3300	890	100	4.7	4.3	4.3	3.2	1.0

TABLE 8

Approximate order of decreasing mobility of leaving groups

$F > NO_2 >> Cl, Br, I, N_3, OSO_2R, -NR_2^+, OAr, OR, SO_2R, NH_2$

TABLE 9



+ pyridine/MeOH

X mobility $NO_2 > F >> Br > Cl > I$

TABLE 10

Activating groups

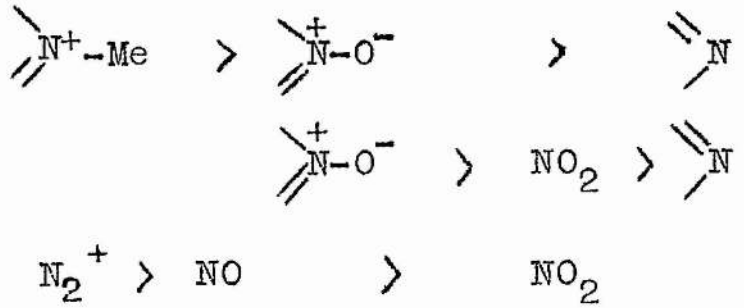


TABLE 11

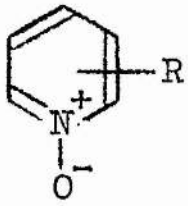
Activating groups in order of decreasing activating power

$-N_2^+$, $-CR_2^+$, $\overset{+}{\underset{//}{\backslash}}NR$, $-NO$, $-NO_2$, $\underset{//}{\overset{\backslash}{N}}$, $-SO_2Me$, $-\overset{+}{N}Me_3$, $-CF_3$, $-COR$, $-CN$, $-COOH$, $-SO_3^-$, $-Cl$, $-Br$, $-I$, $-Ph$.

Deactivating groups (in p-position) in order of decreasing deactivating power.

$-NH_2$, $-OH$, $-NMe_2$, $-OEt$, $-OMe$, $-Me$, $-Bu^t$, $-F$, $-H$.

TABLE 12



+ EtONa/EtOH

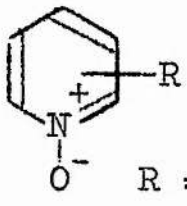
order of reactivity of R 2- > 4- > 3- (↙ inductive effect)

rate of reaction

R =	4-NO_2	4-Br	4-Cl
k =	1100	1.2	1

} at 20°

R =	2-NO_2	4-NO_2	3-NO_2	2-Br	4-Br
k =	6900	660	39	2.20	0.60



+ piperidine/EtOH

R =	2-Br	2-NO_2	4-Br	4-NO_2
k =	7.1	5400	1.9	3.2

the different groups in aromatic nucleophilic substitution. Bunnett et al.[231] studied the "elemental effect" of varying the 1-substituent in a series of 2,4-dinitrobenzenes, with displacement of this 1-substituent by piperidine in methanol, (TABLE 7). Elsewhere[225] he reported a similar order of decreasing mobility (TABLE 8). Parker and Read considered the mobility of the 1-substituent in a series of 2,6-dinitrobenzenes in the presence of pyridine and ethanol (TABLE 9).

Johnson, in a study of the nucleophilic displacement of halogens and nitro-groups from substituted pyridine-N-oxides, has discussed both the general activating effect of the different substituents and structural features, under various conditions (TABLE 10), and also the overall susceptibility of the leaving groups to nucleophilic attack by sodium ethoxide in anhydrous ethanol, and by piperidine in ethanol (TABLE 12). Finally, in this brief review, activating and deactivating groups in aromatic systems have been tabulated by Bunnett, in approximate order of effect (TABLE 11).

The similarity between the kinetic studies (TABLES 7-12) and the experimental work described herein (TABLES 5-6) is now apparent. It must however be emphasised at this point that, although the experimental results now described from the reaction of tervalent

phosphorus reagents with substituted nitrobenzenes do bear a close qualitative relationship with the kinetic studies mentioned briefly in the previous paragraphs, the conditions of reaction are very different and care must be exercised in extrapolating results obtained from, perhaps, o-chloronitrobenzene and piperidine in methanol at 20°, to the corresponding reaction in an excess of triethyl phosphite at 150°. The hypothesis, however, remains useful in this discussion.

(ii) Variations of reactivity of the tervalent phosphorus reagents. Tervalent phosphorus reagents, in particular trialkyl phosphites, have been widely studied as nucleophilic reagents. Kabachnik[237] has quoted the following reactivity series established for the Arbusov reaction, but applicable to other nucleophilic reactions of tervalent phosphorus reagents (R_3P):

reactivity of R_3P: R = alkyl > R = aryl > R = alkoxy

reactivity of phosphites: MeO > EtO > n-PrO > n-BuO

Aksnes,[238] however, has shown that tri-isopropyl phosphite reacts with ethyl iodide considerably faster than does triethyl phosphite, and Mark and Van Wazer[239] have shown that tri-tert-butyl phosphite is probably

the most strongly nucleophilic trialkyl phosphite. These last two results suggest that the nucleophilic reactivity is controlled largely by the combined inductive effects of the substituents, in the absence of any major steric effects. Aksnes[240] has also quoted the relative rates of reaction of different tervalent phosphorus reagents with ethyl iodide at 60°:

Phosphorus Reagent	Ph_3P	Ph_2POEt	$PhP(OEt)_2$	$(EtO)_3P$
10^4k	5.18	2.39	1.79	0.20

The strength of the P=O bond formed has been described already as one of the principal driving forces for these reactions. In this connection it should also be noted that the formation of an extremely stable triphenylphosphine oxide derivative from the reaction of o-dinitrobenzene with ethyl diphenylphosphinite would be likely to increase the vigour of this reaction: this was indeed found to be so.

(iii) Reactions involving aromatic nucleophilic substitution by tervalent phosphorus reagents. (TABLE 5)

The reaction between tervalent phosphorus reagents and o-dinitrobenzene may now be seen to be in close accord with that expected on the basis of general data for

nucleophilic aromatic substitution. As a leaving group, the nitro-group is second only to the fluorine atom in mobility; as an activating group, it is the strongest activating group that is relatively stable under the normal conditions of nucleophilic substutution reactions.[225] Equally important, in the case of reaction with tervalent phosphorus reagents, the two substituents are equivalent in every way: the reaction and products are the same whichever of the two groups is displaced. There is a smooth reaction with trialkyl phosphites in solution to give high yields of the corresponding dialkyl o-nitrophenylphosphonates in the absence of solvent, the reaction is very rapid. There is no evidence for the induction or catalysis of this reaction by light.[241] Diethyl methylphosphonite reacts smoothly to give ethyl methyl-o-nitrophenylphosphinate under milder conditions. This increased activity is as described by Aksnes.[240] A similar reactivity of this reagent has been observed during its use as an agent for the deoxygenation of 2-nitrobiphenyl.[200] The reaction with ethyl diphenylphosphinite is more vigorous still, presumably, as stated already, aided by the considerable stability of the resulting diphenyl-o-nitrophenyl-phosphine oxide.

Trialkyl phosphates, and corresponding compounds containing the P=O group have been recovered from all the reactions described in this section: the origin of the oxygen may be atmospheric, despite the atmosphere of nitrogen in which the reactions are performed, or may be from side-reactions involving deoxygenation of one or more of the nitro-groups in the molecule. The products of this deoxygenation are not formed in sufficient quantity, however, to be isolable from the tarry material also formed in the course of the reaction.

In the reactions with 1,2,4-trinitrobenzene, a considerable acceleration of the reaction is observed, presumably due to the increased activation of the leaving group by the additional nitro-group. This activation is sufficient to maintain nucleophilic aromatic substitution as the favoured reaction path, although there are now further possibilities for reaction (i.e. another reactive nitro-group is present, and the nitro-groups are no longer equivalent). With ethyl diphenylphosphinite, the reaction becomes too vigorous, under the conditions employed, and no products have been isolated.

A similar "over-reactivity" may be the reason for

the poor yield of diethyl o-nitrophenylphosphonate from the reaction of o-dinitrobenzene with O-sodium diethyl phosphite, expected to be a stronger nucleophile than triethyl phosphite in this reaction. It is possible that both nitro-groups are displaced, or that there is interaction with the solvent acetonitrile, or that other products, such as sodium nitrite, interfere with the course of the reaction.

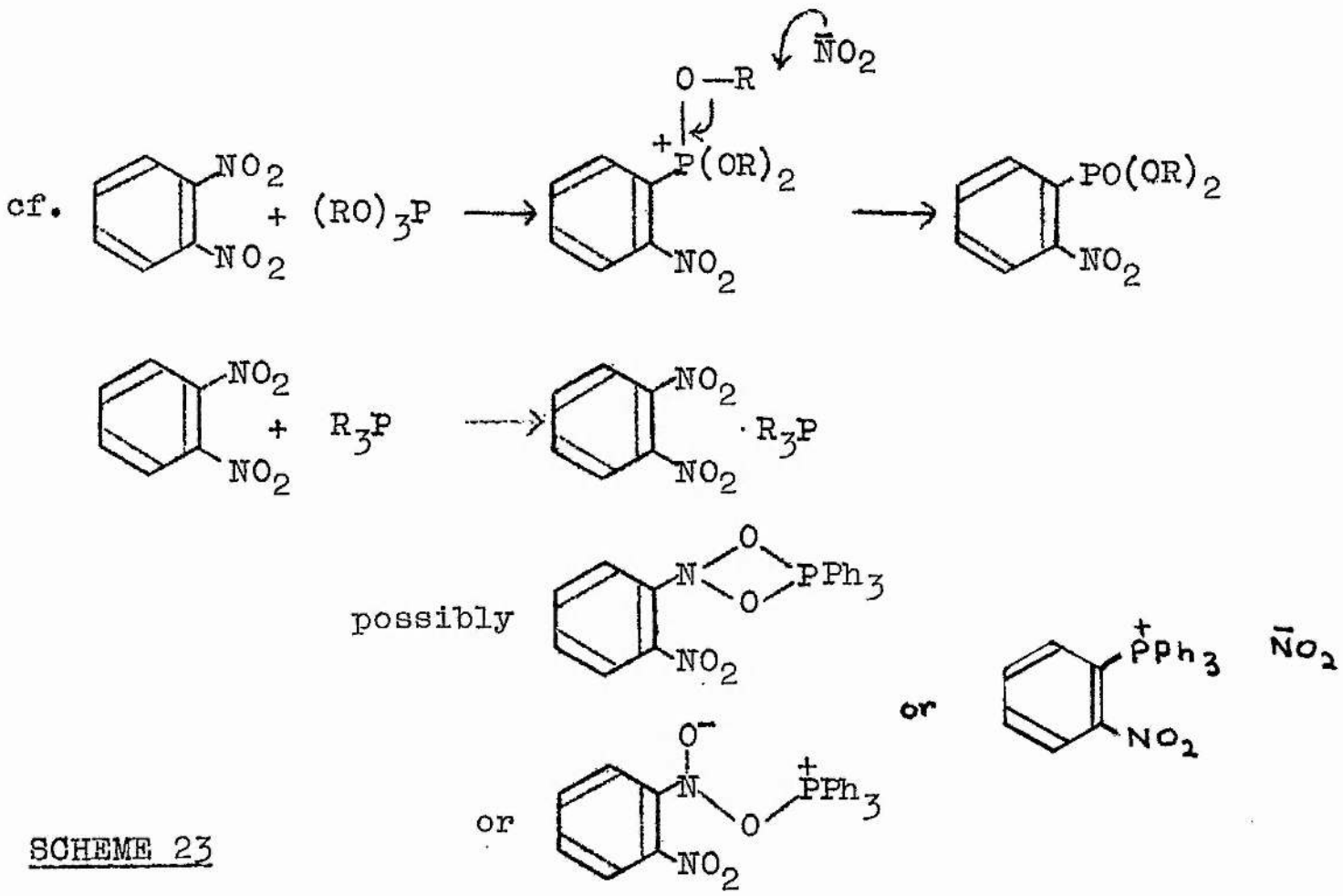
The reaction of 2-nitropyridine-N-oxide with triethyl phosphite gives a good yield of diethyl 2-pyridylphosphonate (102). This is in accord with Johnsons' observations[232] on the high mobility of the 2-nitro-group in substituted pyridine-N-oxides, and with the noted ease of the deoxygenation of such compounds by tervalent phosphorus reagents.[16] The displacement is not observed with triethyl phosphite and 2-nitropyridine: the deoxygenation reaction is therefore presumably preceded by the nucleophilic displacement of the nitro-group.

Chloro-2,4-dinitrobenzene is the only compound found, so far, where the halogen is sufficiently activated to be displaced by triethyl phosphite. However, the activation is insufficient to maintain this as the only reaction path and a number of

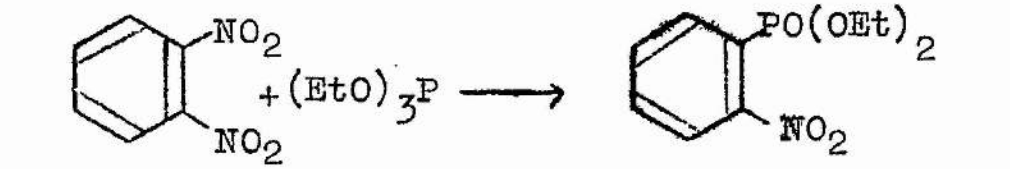
unidentified minor products are formed, presumably by competing deoxygenation reactions.

The reaction of triethyl phosphite with 4-methyl-2'-nitrodiphenylsulphone is similar to that described above. Although the greater part of the reaction mixture becomes a viscous tar, a low yield of diethyl o-nitrophenylphosphonate has been isolated; this is presumably formed by nucleophilic displacement of the arylsulphonyl group. The mobility of this group is, however, considerably less than that of the nitro-group.

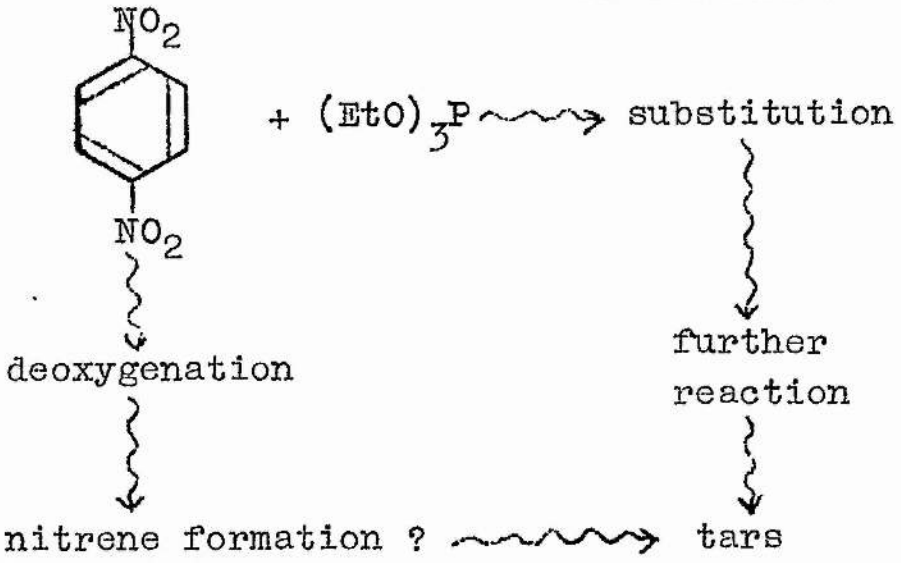
(iv) Reactions not showing aromatic nucleophilic substitution by tervalent phosphorus reagents. (TABLE 6) The failure of nitrobenzene, m-dinitrobenzene, o-chloronitrobenzene, 2-nitropyridine and 4-nitropyridine-N-oxide to react with a variety of tervalent phosphorus reagents by the process of aromatic nucleophilic substitution, may be safely ascribed to the lower mobility of the potential leaving groups (TABLES 7-12). As was stated earlier, if there is insufficient activation of the "replaceable" group, then no displacement reaction will occur. Further, in reactions with tervalent phosphorus reagents, other routes will then increase in importance to give a variety of



SCHEME 23



no further reaction



SCHEME 24

products. That this is so, is evinced by the quantity of tarry materials found in these "unsatisfactory" reactions.

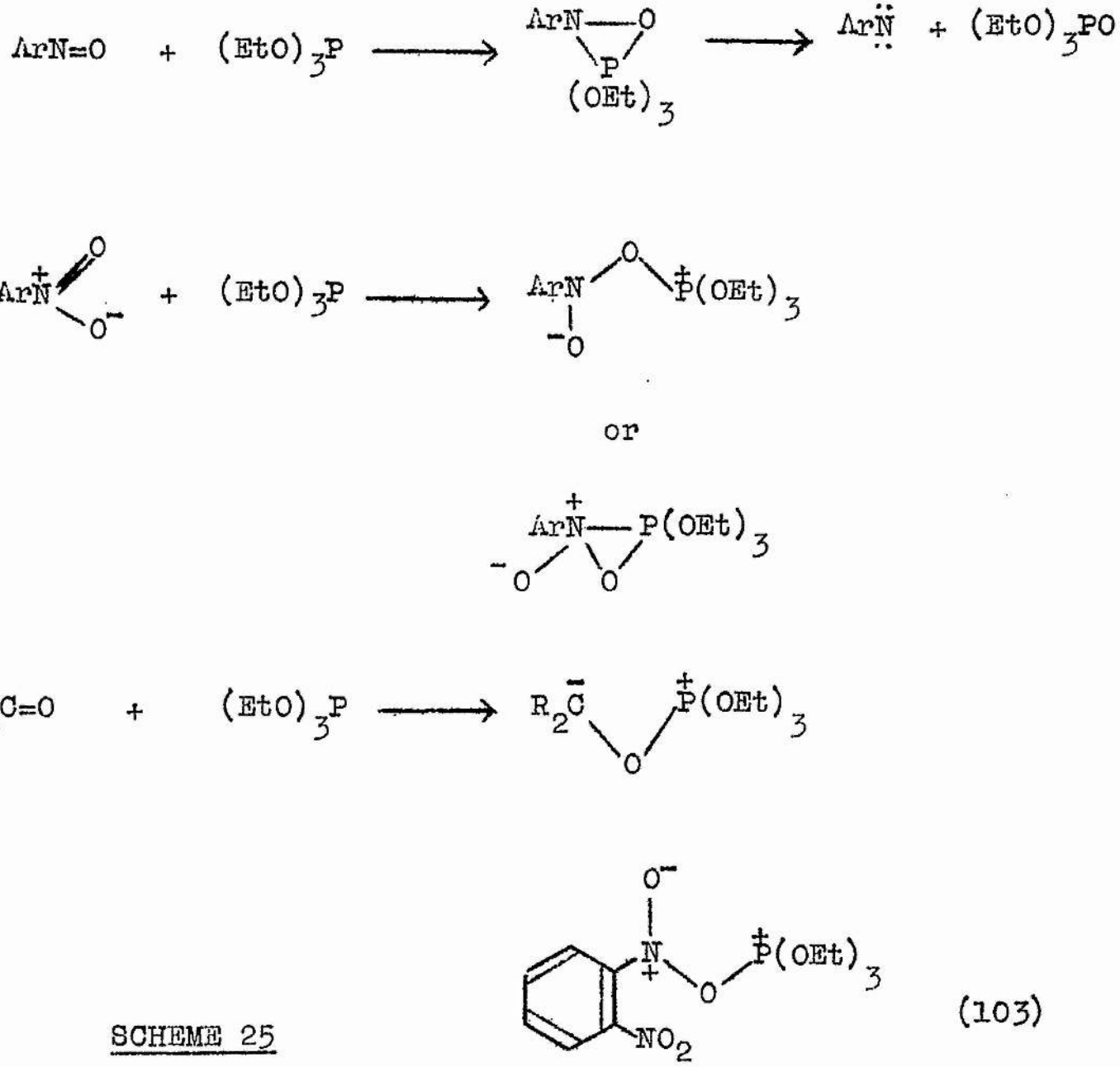
In the case of the attempted reaction with o-nitrobenzenediazonium fluoroborate, the diazonium salt group, although the strongest of the activating groups, does itself decompose vigorously in the presence of tervalent phosphorus reagents. Thus aromatic nucleophilic substitution is unlikely to take place.

Triphenyl- and tributylphosphine, despite their greater nucleophilicity, would be expected to give 1:1 adducts with polynitrobenzenes, (cf. Horner[164]), rather than to show this form of nucleophilic substitution. They would not, moreover, be able to undergo the final dealkylation to the P=O compound, with the loss of a substituent in conjunction with the nitrite leaving-group (Scheme 23).

The various reactions, or lack of reaction, with p-dinitrobenzene are more difficult to explain. The reasoning as to mobility, activation and "equivalence" of the two groups is as for o-dinitrobenzene. The reactions would therefore be expected to follow similar courses. Two further possibilities arise, however.

Firstly, following a possible nucleophilic displacement of one nitro-group, the second nitro-group might still be vulnerable to attack by the excess of the tervalent phosphorus reagent to give either further nucleophilic substitution or deoxygenation to the nitrene, with all the possibilities that that would entail, (Scheme 24). In the case of o-dinitrobenzene it may be argued that the second nitro-group is shielded from further attack by the adjacent diethyl phosphonyl group; the fact that the product is recoverable at all from an excess of triethyl phosphite under reflux is some evidence for this.

Secondly, such discrepancies in the behaviour of o- and p-substituted compounds have been observed previously in attempted nucleophilic aromatic substitutions. Bunnett[225] reported that, while the hydrolysis or methanolysis of a number of o- and p-substituted benzene derivatives was succesfully accomplished, in the reaction of p-nitrobenzonitrile, the nitro-group was largely reduced, rather than replaced, by the excess of ethoxide. Similarly, while sodium sulphide acted on o-dinitrobenzene to produce either the o-nitrothiophenoxide ion or the symmetrical sulphide or disulphide, the corresponding reactions



SCHEME 25

(103)

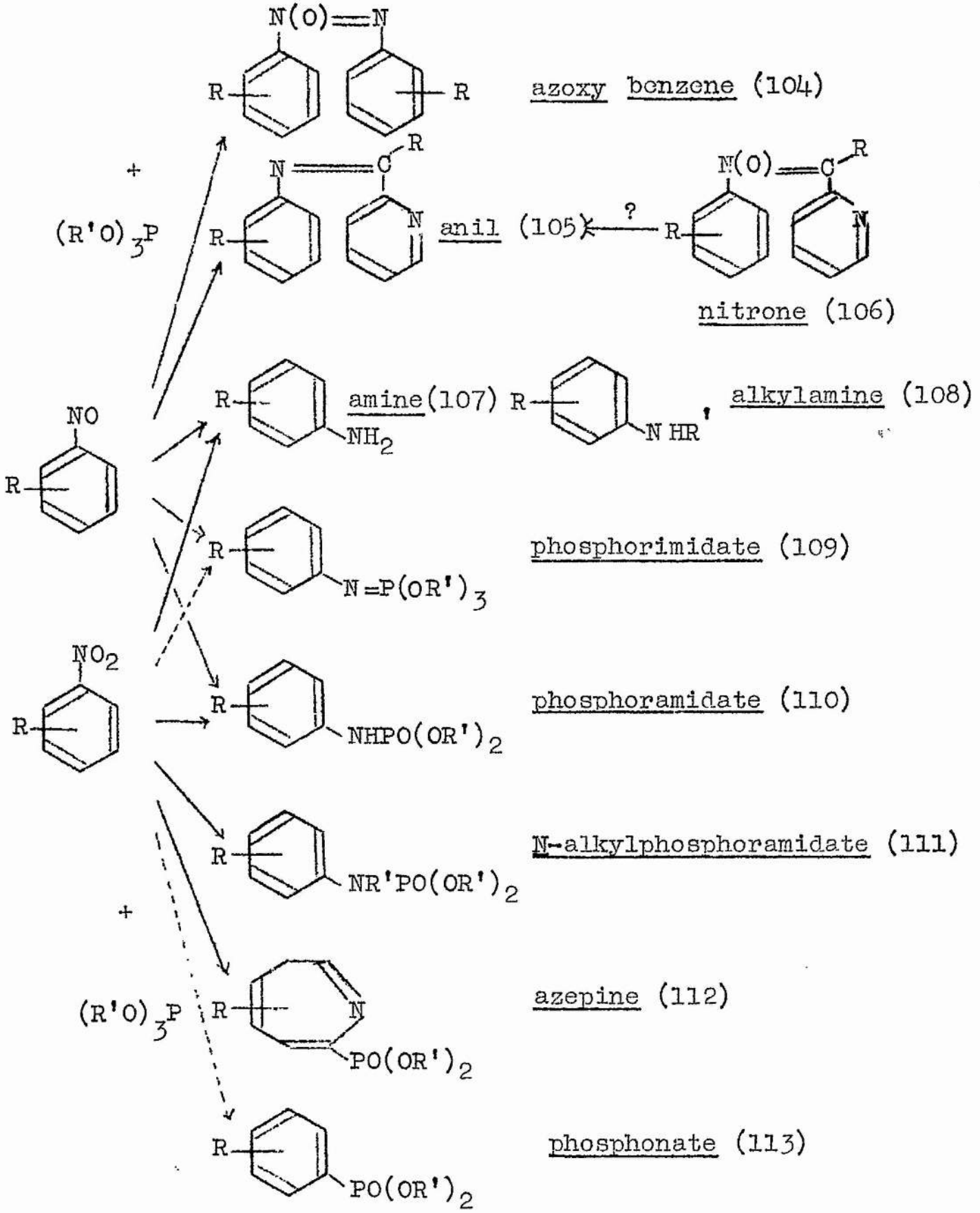
with p-dinitrobenzene again led to reduction of the nitro-group.

(v) Other possible mechanisms. The lack of aromatic nucleophilic substitution in the reaction with p-dinitrobenzene compared to the more successful reactions with o-dinitrobenzene, 1,2,4-trinitrobenzene and 2-nitropyridine-N-oxide, suggests that the nitro-group and the N-oxide function adjacent to the displaced nitro-group may have some importance over and above their activating effect. In all other reactions of tervalent phosphorus reagents, so far considered, with aromatic nitroso-, nitro- or carbonyl compounds, initial attack at the oxygen atom by phosphorus has been suggested (Scheme 25).[17,44,149] The formation of a nitrene intermediate has been proposed for a variety of reactions with aromatic nitro-compounds,[17] yet there seems to be no indication of its participation in the reactions of o-dinitrobenzene with tervalent phosphorus reagents. It has now been shown, in the latter half of the experimental work described herein, that an unactivated nitro-group (e.g. in p-nitrotoluene) may also be displaced by tervalent phosphorus reagents: there seems to be no likelihood of aromatic nucleophilic substitution in this latter case (a mechanism involving

attack on an oxygen of the nitro-group, followed by rearrangement through a four-membered-ring intermediate, is discussed in the following chapter). However, while it may be possible to formulate intermediates (103) resulting from attack by the phosphorus on an oxygen of the nitro-group, there is much greater difficulty in postulating a reaction mechanism that would lead from this intermediate to the products which have been isolated from the reaction. It may be that an investigation in detail of the minor products of the reaction, and of the kinetics of the reaction, will differentiate more clearly between the various possibilities of mechanism for this reaction.

2. Reactions of o-Alkylnitroso- and Alkylnitrobenzenes with Tervalent Phosphorus Reagents.

The reactions of a range of o-alkylnitroso- and alkylnitrobenzenes with tervalent phosphorus reagents have now been studied. In contrast to the corresponding reactions of o-dinitrobenzene and related compounds, these reactions give rise to a number of different products, frequently in low yield, and also to a considerable quantity of, as yet, unidentified tarry material. Such behaviour may indicate the participation



Summary of products found.

SCHEME 26

of one or more reactive intermediates, and it is upon these possible intermediates and upon the overall mechanism of the reactions, that interest centres. The preparative aspects of these reactions will be discussed briefly.

An outline of the types of products formed is given in Scheme 26. The yields of these products, from particular reactions, are detailed in TABLES 13 and 14.

The reactions show many products in common, and the nature of these products is not, in general, affected by a change in the alkyl substituent in the aromatic system. The products will, therefore, be considered together, where applicable, under the generic names at the head of the columns in TABLES 13 and 14, with structures as shown in Scheme 26. Thus the 'phosphoramidate' (110) and the 'azepine' (112) from the reaction of trimethyl phosphite with o-nitrotoluene, for example, should be understood to be dimethyl N-o-tolylphosphoramidate and dimethyl 2-methyl-3H-azepin-7-ylphosphonate, respectively. Full structures and nomenclature will, of course, be given where necessary.

In general, the products (104-112) are consistent with the hypothesis that a nitrene intermediate is

TABLE 13

Nitroso-Benzene	Phosphorus Reagent	Solvent	Azoxy Benzene (104)	Anil (105)	Phosphor-imidate (109)	Phosphor-amidate (110)
o-Me	$(EtO)_3P$	benzene	46%	3-5%		5%
o-Me	$(EtO)_3P$	$(EtO)_3PO$	3.1	18	16%	10.5
o-Et	$(EtO)_3P$	benzene	49	5		
o-Et	$(EtO)_3P$	$(EtO)_3PO$	7	19	20.5	9.1

TABLE 14

Nitro-benzene	Phosphorus Reagent	Phosphor-amidate (110)	N-alkyl phosphor-amidate (111)	Azepine (112)	Phosphonate (113)
o-Me	$(EtO)_3P$	25%	13.5%	8.5%	0
o-Me	$(MeO)_3P$ *	5.3	30.0	17.8	0
o-Et	$(EtO)_3P$	23.3	9.7	7.3	
p-Et	$(EtO)_3P$	20-26	21-23	3	5-7%
p-Me	$(EtO)_3P$	26	24	6	5
p-Me	$(MeO)_3P$ *	5.4	26	8.6	0
m-Me	$(EtO)_3P$	(22)	(27)	0	0
m-Me	$(MeO)_3P$ *	(8.5)	(12)	(?)	0
o-OMe	$(MeO)_3P$ *	(12)	(26)	(?)	(2.5)
p-OMe	$(MeO)_3P$ *	13	16	15	3.0
p-OMe	$(EtO)_3P$	(16)	(23)	(?)	(6.0)

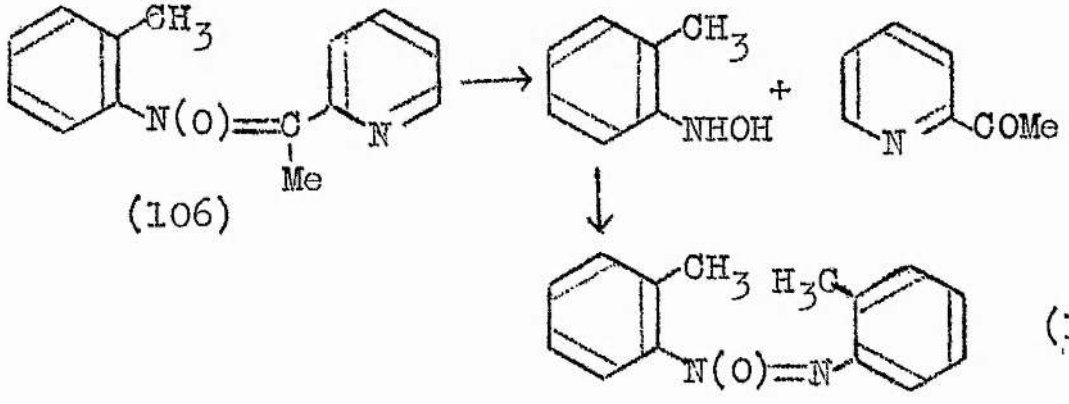
*yields based on reacted nitro-compound (70-90% of total.)

( ) g.l.c. estimates and analysis only - not confirmed by i.r. analysis.

formed during the course of the deoxygenation reaction. In addition, a novel displacement of the nitro-group from p-nitrotoluene and related compounds is reported: in these cases there appears to be no necessity for nitrene participation, and a mechanism involving a four-membered intermediate is proposed, the products being the corresponding dialkyl arylphosphonates (113).

(a) Preparative aspects of the reaction with o-alkylnitrosobenzenes. The results of earlier investigations[72] of the reactions of tervalent phosphorus reagents with alkylnitroso-compounds are confirmed. Triethyl phosphite reacts smoothly with equimolar quantities of o-alkylnitrosobenzenes in benzene solution at 0° to give good yields (45-50%) of the corresponding 2,2'-dialkylazoxybenzene (104). In addition, the anil, N-o-alkylphenyl-2-alkimidylpyridine (105),[73] is formed in smaller amounts (3-5%), together with a similar yield (5%) of the dialkyl N-arylphosphoramidate (110). As the ratio of triethyl phosphite to nitroso-compound increases, so the trialkyl N-arylphosphorimidate (109, 16-20%), dialkyl N-arylphosphoramidate (110, 9-11%) and the anil (105, 18-19%) are formed at the expense of the azoxybenzene (104, 3-7%). There is no evidence, however, for an abrupt

change of mechanism between the two extremes of reaction conditions.[72,73] The azoxybenzene is present, in small amounts, even in the vigorous reaction of o-alkylnitrosobenzenes with an excess of triethyl phosphite in triethyl phosphate solution. There is no evidence for the formation of the nitrone, N-(o-alkylphenyl)α-alkyl-β-(2-pyridyl)nitrone (106),[73] either by g.l.c. or by product analysis. In the light of these latter statements, it appears to be unnecessary to suggest, as does Sundberg,[73] that, in the reaction of o-nitrosotoluene, the azoxybenzene (104) arises by disproportionation of o-tolylhydroxylamine, formed in turn by the hydrolysis of the nitrone during the investigation of the reaction mixture. The azoxybenzene is, in fact, a primary product of the reaction.



o-Alkylanilines (107) are formed in low yields (7%). While other low boiling, minor, products are observed by g.l.c., they have not been characterised further.

Such a study has, however, been reported elsewhere.[73]

(b) Preparative aspects of the reaction with alkylnitrobenzenes. The reaction of alkylnitrobenzenes with tervalent phosphorus reagents under far more vigorous conditions (heating under reflux in an excess of the phosphorus reagent for 14-17 hours) gives a range of products different from that described above. In addition, there is a significant variation in the yields of the various products, dependent upon the phosphorus reagent used.

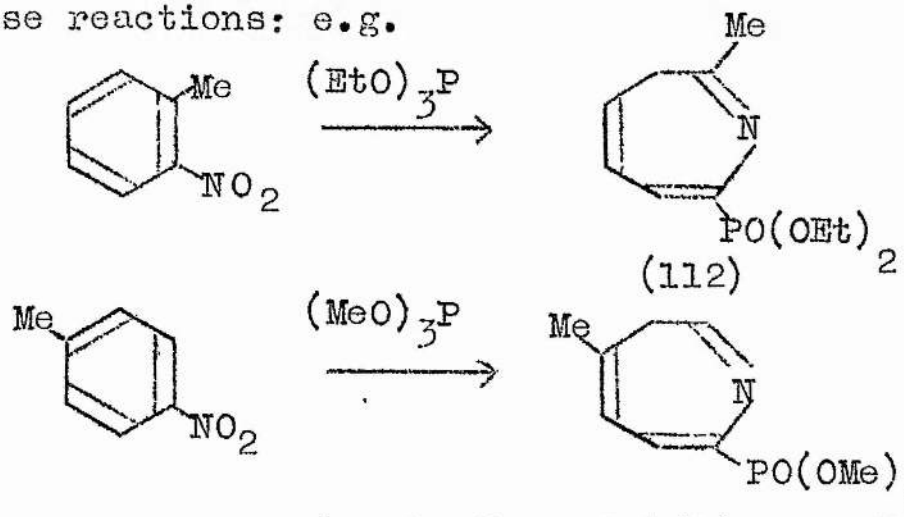
There is no evidence for the presence of trialkyl N-arylphosphorimidates (109) in the reaction mixture, at the completion of the reaction under the conditions described. Equally, it must be stated that the positive identification of a trialkyl N-arylphosphorimidate (109) in the presence of the corresponding dialkyl N-alkyl-N-arylphosphoramidate (111) and the dialkyl N-arylphosphoramidate (110), by either i.r. or n.m.r. spectral analysis is extremely difficult, owing to the similarity of the various spectra. Reports[73,200] that phosphorimidates have been identified by g.l.c. must be subject to some doubt, in view of the ready thermal rearrangement of the phosphorimidate to the N-alkylphosphoramidate, as described earlier. However, all this does not

preclude the possibility of their formation, and subsequent rearrangement or further reaction, during the course of the deoxygenation reaction. (Sundberg was able to isolate relatively pure samples of trialkyl N-arylphosphorimidates from similar reactions after heating under reflux for 4 hours only.[73])

The main products of this series of reactions are the dialkyl N-arylphosphoramidates (110) and the dialkyl N-alkyl-N-arylphosphoramidates (111): the ratio of these varies considerably, however, with the phosphorus reagent used. Thus triethyl phosphite, with o-, m- and p-alkylnitrobenzenes, gives approximately equal amounts of the phosphoramidate (110, 16-25%) and the N-alkylphosphoramidate (111, 10-27%), while trimethyl phosphite gives small quantities only of the former (110, 5-13%) and the N-alkylphosphoramidate becomes the major product (111, 12-30%). The reaction with trimethyl phosphite is considerably less vigorous than that with triethyl phosphite: the reaction mixture may remain clear for up to 60 minutes under reflux, whereas that with triethyl phosphite darkens at once at ca. 60° and becomes increasingly tarry. As a consequence of this, however, and of the tendency of trimethyl phosphite to isomerise rapidly to dimethyl

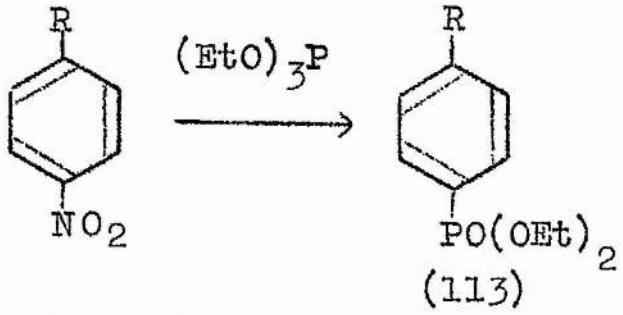
methylphosphonate,[43] considerable amounts (10-30%) of the unchanged nitro-compound have been found at the end of each reaction. In these cases yields of products have been calculated on the basis of the quantity of nitro-compound that has been consumed.

In addition to these major products, two series of minor products have been isolated and characterised. Firstly, compounds identified as the appropriate azepines (112) have been recovered from a number of these reactions: e.g.



In some cases, owing to the solubility of the azepine in water, extraction from the other products is extremely rapid. In other cases, extraction by dilute acid, followed by chromatography on alumina, proves more successful.

Secondly, a minor product, in certain reactions only, is now identified as the dialkyl arylphosphonate (113).



R = Me, Et, OMe

(113)

While this has no preparative significance (3-6% yields), the mechanism is of greater interest, and will be discussed shortly.

Low-boiling products, anilines and alkylated anilines, are present in the final reaction mixture. These have not, however, been studied systematically in the present investigation. A liquid-air cold-trap, as used to condense ethyl nitrite in earlier experiments, collected, instead, a considerable quantity of ethylene from the reaction of triethyl phosphite with p-methyl- and p-ethylnitrobenzene.

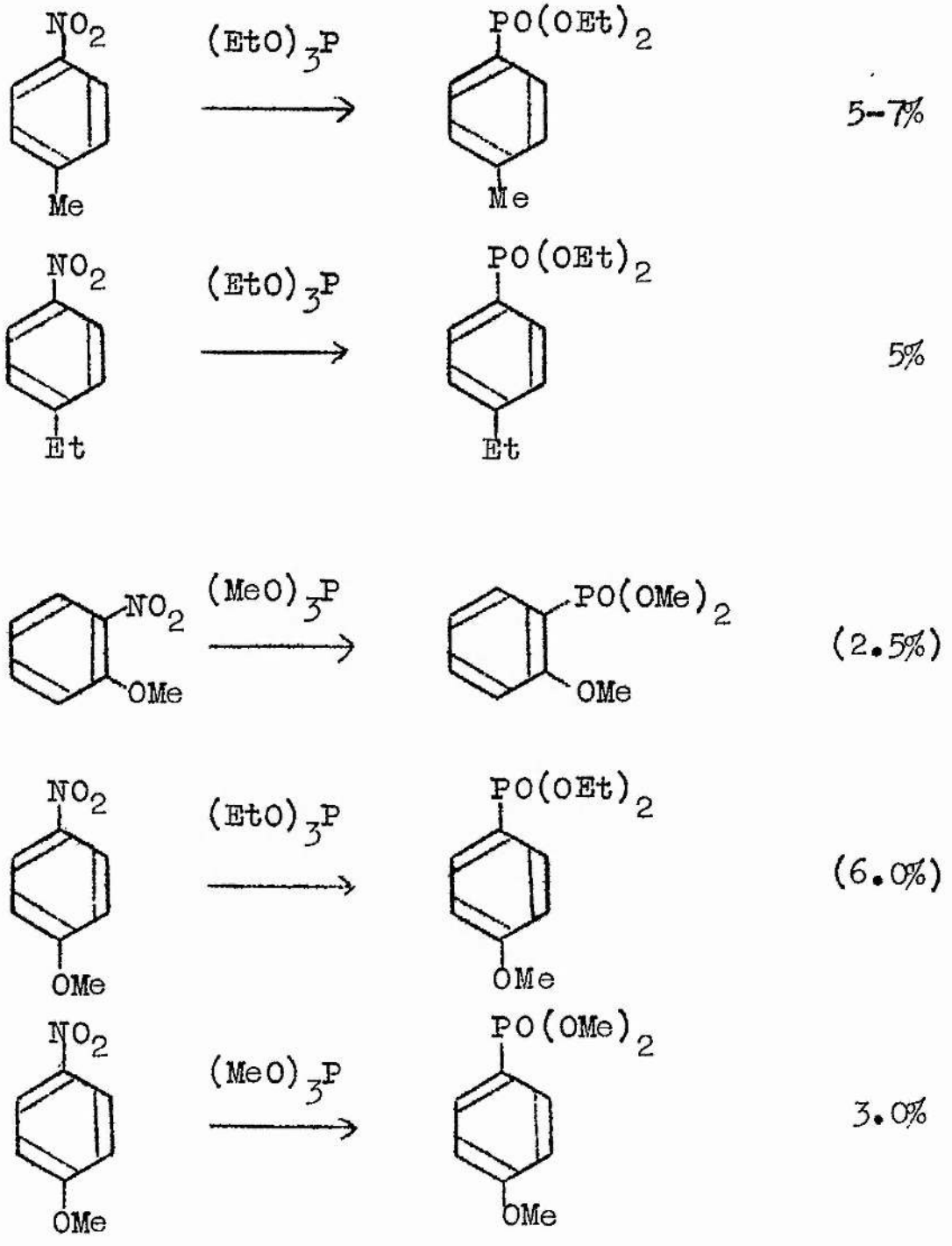
In all these reactions, the overall accountancy of products is low, rarely exceeding 60%. Tar formation increases the difficulties of separation of the various products and severely limits any attempt to determine the fate of all the starting reagents.

A number of reactions, (those with the yields in parentheses in TABLE 14), were examined briefly by g.l.c. alone, by comparison of the retention times of the various products with those of authentic samples on two different

columns. While it is reasonable to suppose that the reactions are analogous, and that the products and authentic samples do correspond correctly, this cannot be described as certain until the individual products have been isolated and identified by comparison of their i.r. and n.m.r. spectra.

Unfortunately, owing to the high boiling-point of many of the products of these reactions, and to the tendency of these products to decompose or to rearrange at high temperatures, preparative-scale g.l.c. is, as yet, largely impossible.

(c) The mechanism of the novel nitro-group displacement. When this investigation was undertaken, it was supposed that the reactions of the aromatic nitro-compounds with tervalent phosphorus reagents that were to be studied, would, in general, give evidence for or against the participation of a nitrene intermediate in a variety of deoxygenation reactions. However, as has been described already, in some detail, the reaction with o-dinitrobenzene and related compounds gives, apparently, a novel example of aromatic nucleophilic substitution by the phosphorus reagent, with complete loss of the nitro-group as nitrite ion, and with no question of nitrene participation.



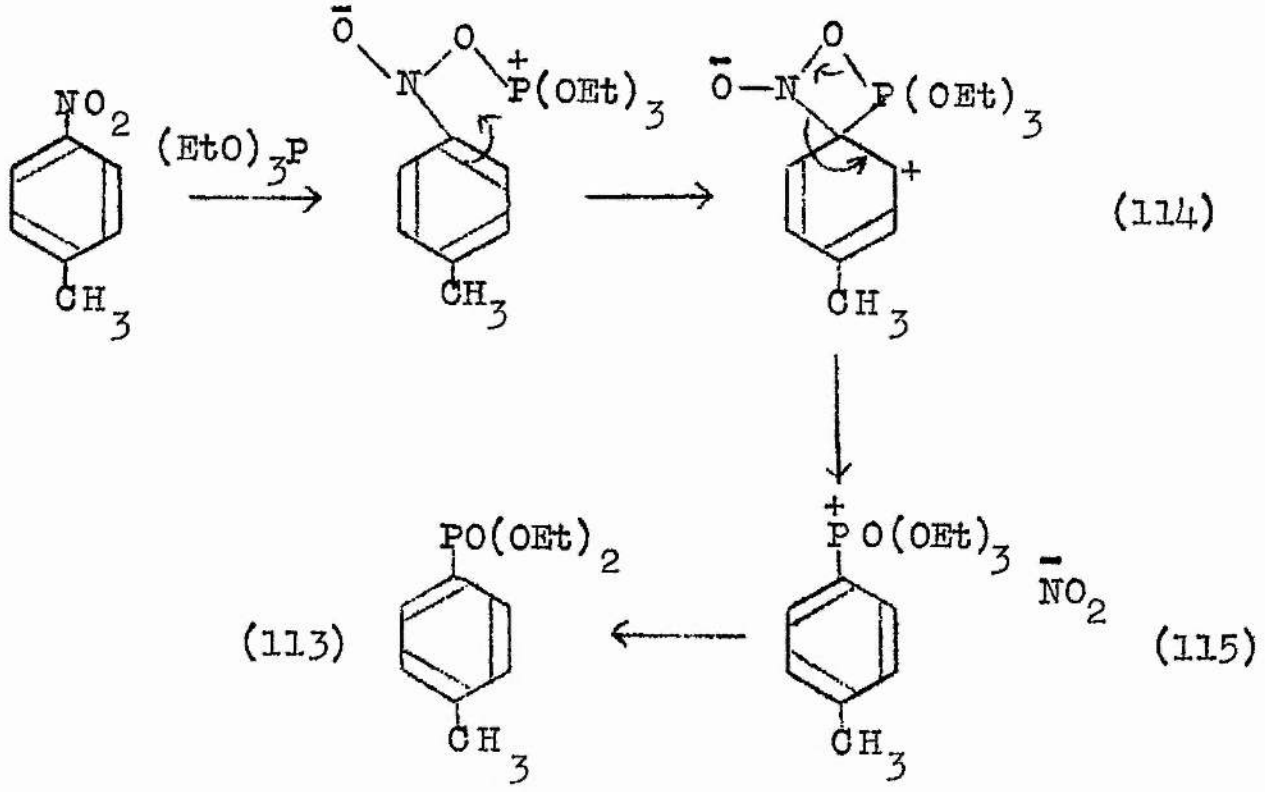
( ) g.l.c. results only

SCHEME 27

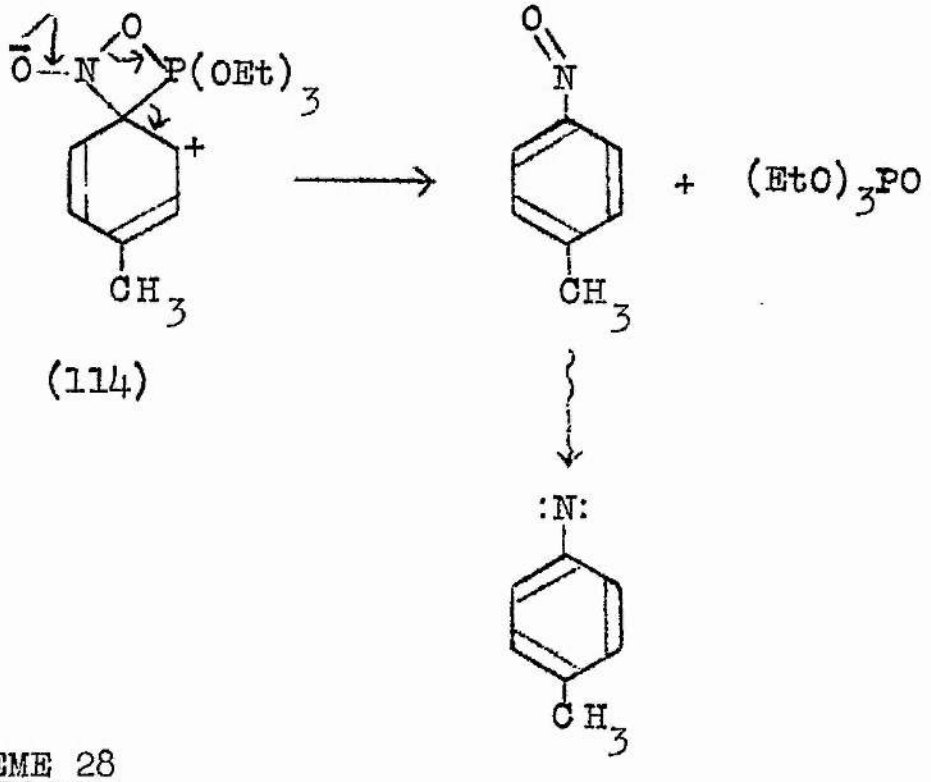
In the reactions of alkylnitrobenzenes with triethyl and trimethyl phosphite, the greater part of the reaction products do indicate nitrene participation in a deoxygenation reaction: these reactions will be discussed in the following section. However, in those reactions described in Scheme 27, a superficially similar displacement of the nitro-group takes place, to give the corresponding dialkyl arylphosphonate (113). In these cases, there seems to be little possibility of aromatic nucleophilic substitution: as has been shown already (TABLE 11), p-methyl and p-ethyl groups are deactivating towards such substitutions. Although the displacement of the halogen from p-chlorotoluene by sodium methoxide has been reported,[243] the conditions of the reaction (sealed tube, 150°, no solvent) indicate the difficulty of effecting such a substitution.

There is no evidence for the induction or catalysis of the reactions by light, the dialkyl arylphosphonates being formed to the same extent in complete darkness, as in normal daylight, and not at all in the presence of ultra-violet light at 20°.

Repeating the experiments with o- and p-nitroanisole, in place of o- and p-nitrotoluene, gives no significant change in the yield of the phosphonate. However,



alternative collapse of intermediate (114)



SCHEME 28

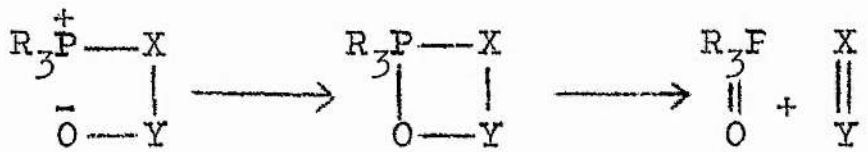
while the phosphonate is formed in the reaction of triethyl phosphite with both p-nitrotoluene and p-nitroanisole, in the corresponding reactions of trimethyl phosphite it is formed only in the reaction with p-nitroanisole: the formation of more than 0.5% of dimethyl p-tolylphosphonate would be detected.

A mechanism for this reaction is suggested in Scheme 28. Nucleophilic attack on the oxygen atom has already been discussed as the initial stage of most deoxygenation reactions of tervalent phosphorus compounds. The phosphorus atom is now electrophilic, rather than nucleophilic, and, in the absence of bulky o-groups which might give rise to steric hindrance, is free to move into a position such that electrophilic attack on the aromatic ring, with the resultant formation of a four-membered intermediate, is favoured. Subsequent collapse of this intermediate leads to the observed products.

Unfortunately, there is no evidence, as yet, as to the fate of the displaced nitro-group. An attempt to condense ethyl nitrite from the volatile products of the reaction, as described previously for the reactions of o-dinitrobenzene, resulted in the collection of a quantity of ethylene, thought to arise in the formation

of the azepine compound, but no ethyl nitrite, on the basis of vapour-phase i.r. spectra.*

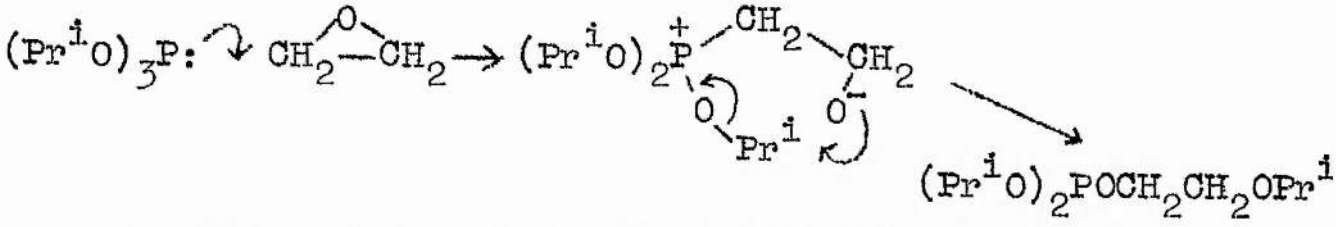
Two further points must be made. If the intermediate (114) is formed, then the alternative collapse to the nitroso-compound and triethyl phosphate could occur as a competing reaction. The nitroso-compound would, of course, react at once with the excess of triethyl phosphite. Also the analogy with the basic Wittig reaction is not complete, the four-membered ring in such a reaction being formed normally from a dipolar betaine with rearrangement of this to give a P=O compound and an unsaturated X=Y linkage:



When trialkyl phosphites have been used in place of the more usual triphenylphosphine the reaction has taken a different course, owing to the ready dealkylation of the betaine intermediate:[244]

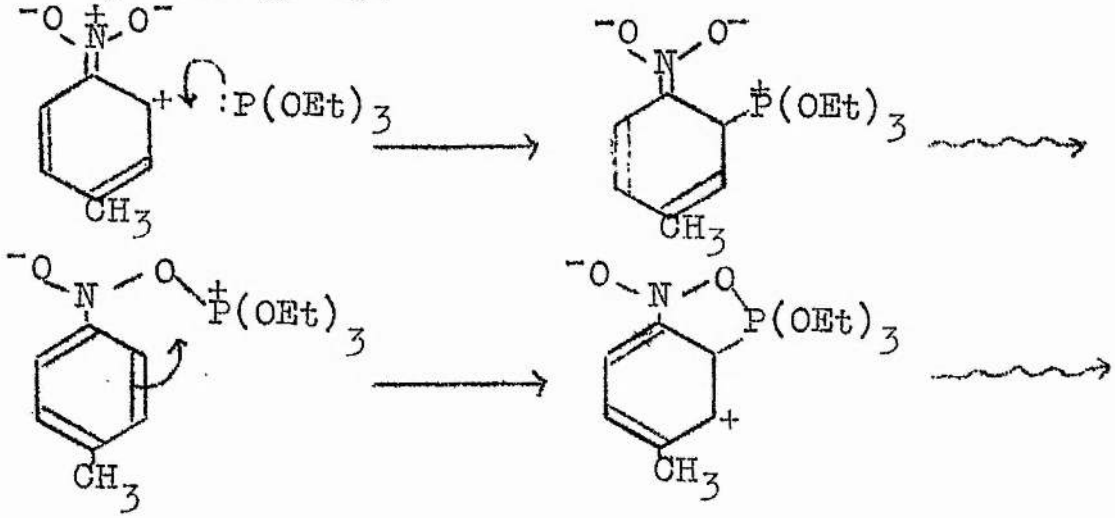
*A very recent report[250] describes the deoxygenation of alkyl nitrites by tervalent phosphorus reagents: this may, therefore, account for the lack of evidence for the formation of this compound.

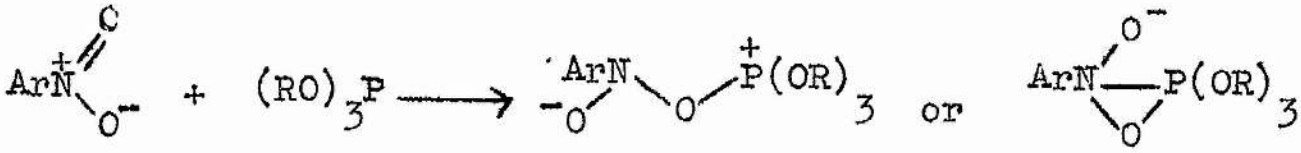
e.g. for dealkylation of a betaine intermediate:

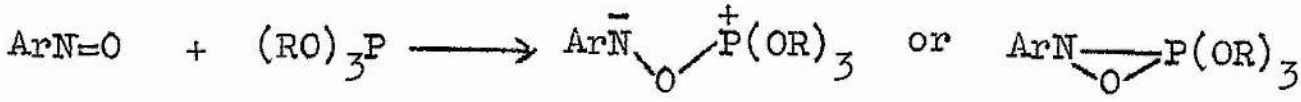


The formation of the phosphonates in the reaction of trimethyl phosphite with p-nitroanisole (but not with p-nitrotoluene), and in the reaction of triethyl phosphite with p-nitrotoluene (but not with m-nitrotoluene) is, however, consistent with the theory of electrophilic attack by the phosphorus atom on the aromatic ring.

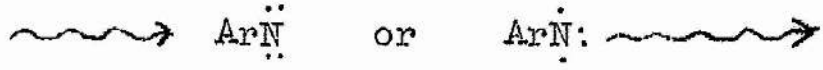
Also, the fact remains that the displacement does take place, and that, on the basis of g.l.c., i.r. and n.m.r. studies, the p-substituted nitrobenzenes give the corresponding p-substituted phenylphosphonates. Thus there is, in these cases, little likelihood of attack by phosphorus on the ring carbon atom adjacent to the displaced group:

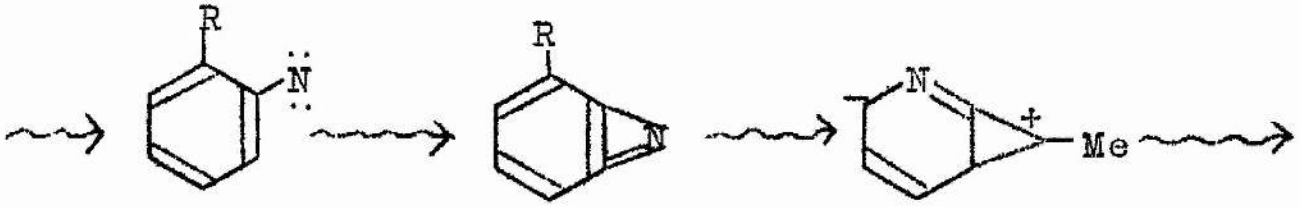


(i) 



(ii) 

(iii) 

(iv) 

(v) formation of products (104-112) from these intermediates.

SCHEME 29

Further clarification of the mechanism of this novel reaction is therefore required.

(d) The mechanism of the deoxygenation reaction.

The remaining products of the deoxygenation of aromatic nitroso- and nitro-compounds by tervalent phosphorus reagents can be accounted for, partially at least, on the basis of participation by a reactive intermediate, such as the nitrene, in the reaction. In no case, other than that described above, is there any evidence for the loss of nitrogen from the aromatic system. Any investigation of this reaction should consider the following aspects of the mechanism (Scheme 29):

(i) the nature of the "primary adduct",

(ii) the possible intermediacy of the nitroso-group, or of its adduct with the phosphorus reagent, formed by deoxygenation of the nitro-group, or of its adduct with the phosphorus reagent,

(iii) the formation of a nitrene, as a reactive intermediate,

(iv) the possible rearrangement of this nitrene, if formed, to other reactive intermediates,

(v) product formation from these possible intermediates.

Each of these will therefore be considered in turn, necessarily briefly.

(i) Nature of the primary adduct. While dipolar or cyclic adducts between tervalent phosphorus reagents and aromatic nitroso- and nitro-compounds, as shown in Scheme 29(i), have been proposed by a number of workers,[17,86,149] there are as yet no reports of the isolation of such intermediates, or of any physical evidence for their existence. In the light of recent reports[42,53-62] of the isolation of stable adducts between tervalent phosphorus reagents and various carbonyl compounds, this lack may soon be remedied. At present, while it may be reasonable to suppose that such 1:1 adducts are formed, any discussion as to their stability or precise nature must remain tentative.

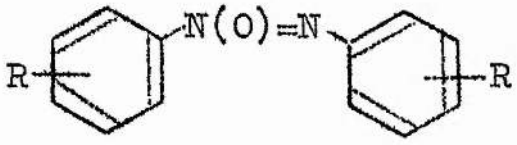
(ii) The possible intermediacy of the nitroso-group, following deoxygenation of the nitro-group, or the adducts thereof. The report of Katritzky (85-87)[144] of the intermediacy of a nitroso-compound in one particular reaction of a nitro-compound with triethyl phosphite has been described already (p.33). Allen[149] has referred to the appearance of a trace of blue-green colouring, during the deoxygenation of α-halonitro-compounds with triethyl phosphite. Todd,[200] however,

was unable to trap an intermediary nitroso-compound in the deoxygenation of 2-nitrophenyl phenyl sulphide by triethyl phosphite in the presence of trans-stilbene, which might have been expected to give the corresponding azoxy compound, from the reaction of the olefin with the nitroso-compound.

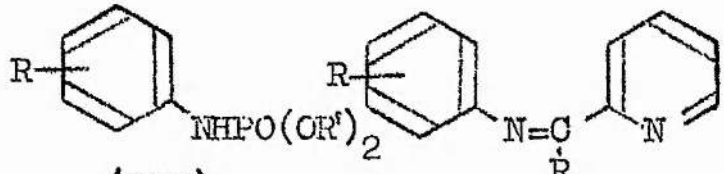
The reaction of tervalent phosphorus reagents with alkylnitrosobenzenes (hydrocarbon solution, 0°, ca. ½ hour) is certainly considerably more rapid than the corresponding reaction with alkylnitrobenzenes (excess phosphorus reagent, 150°, 14 hours). Any nitroso-compounds formed by the deoxygenation of the nitro-compounds would have extremely short existences under these latter vigorous conditions.

Product analysis does not, at first, suggest the intermediacy of the nitroso-compounds in nitro-group deoxygenations. The formation of azoxy-compounds (104) in high yields from aromatic nitroso-compounds, without any phosphorimidates (109) or phosphoramidates (110,111), is in considerable contrast to the range of products isolated from the reactions with aromatic nitro-compounds. However, this is largely a result of the conditions under which the different reactions have normally been performed. Under controlled conditions

in benzene solution at 0°, trialkyl phosphites react with the excess of the nitroso-compound, with no incorporation of the phosphorus moiety into the final product. It is now shown however, that even under these conditions, a trace of the dialkyl N-arylphosphoramidate (110) is formed, together with a trace of the anil (105), which requires a more extensive skeletal rearrangement.



(104)



(110)

(105)

With an increase in the ratio of phosphorus reagent to nitroso-compound, so the proportion of phosphorus-containing products increases. The yield of the anil also increases at first, again at the expense of the azoxy-compound (104), but this too may be expected to decrease as the conditions of the experiment become more vigorous and there is a decrease in the time available for such a rearrangement to occur. If this is so, then the product distribution will resemble that from the reaction of aromatic nitro-compounds with tervalent phosphorus reagents.

This parallels the results of Bunyan and Cadogan[72]

from the reaction of N,N-dimethyl-p-nitrosoaniline with triethyl phosphite, which gave products which varied directly with the quantity of phosphorus reagent used, as expected on the theory of the participation of a resonance-stabilised nitrene intermediate.

The addition of the nitroso-compound to a large excess of the phosphorus reagent at the boiling-point might be expected to yield a product distribution identical with that from the reaction with aromatic nitro-compounds. It would, however, be an exceedingly violent reaction and extensive charring of products, at the least, would be expected to follow.

(iii) The formation of a nitrene, as a reactive intermediate. Although mechanisms have been proposed, as described earlier,[70,86,132,133] which do not, in particular reactions, require a nitrene intermediate, the greater part of the experimental evidence is in favour of this hypothesis.

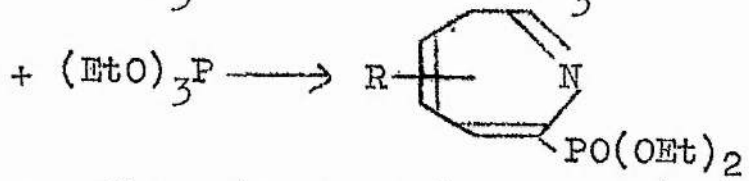
The typical reactions of a nitrene intermediate generated by the thermal or photolytic decomposition of aryl azides, and by other methods, have been described earlier. The products obtained by the deoxygenation of an aromatic nitroso- or nitro-compound by tervalent phosphorus reagents show in many cases a close resemblance

to those obtained in the corresponding azide decompositions. The formation of amines suggests hydrogen-abstraction, either from a side chain or from other reactants present. The formation of quantities of tarry material suggests that some such random reaction has been in operation. The formation of trialkyl N-aryl-phosphorimidates, presumably by direct reaction of the trialkyl phosphite with the nitrene, parallels the preparation of these compounds by the decomposition of the aryl azide in an excess of the phosphite reagent.[189] Finally, the formation of azepine systems, in the presence[140] or absence[146,200] of diethylamine, completes the analogy with accepted examples of the behaviour of nitrene intermediates:[119,125-126]

$$ArN: + ArH \longrightarrow ArNH \xrightarrow{ArH} ArNH_2$$

residual radicals ⟿ tars

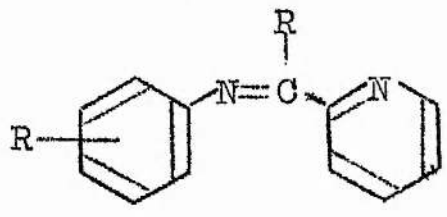
$$+ (EtO)_3P \longrightarrow ArN{=}P(OEt)_3$$



However, there is, as yet, no spectral evidence for the existence of the nitrene intermediate under these conditions, as there is for the thermal and

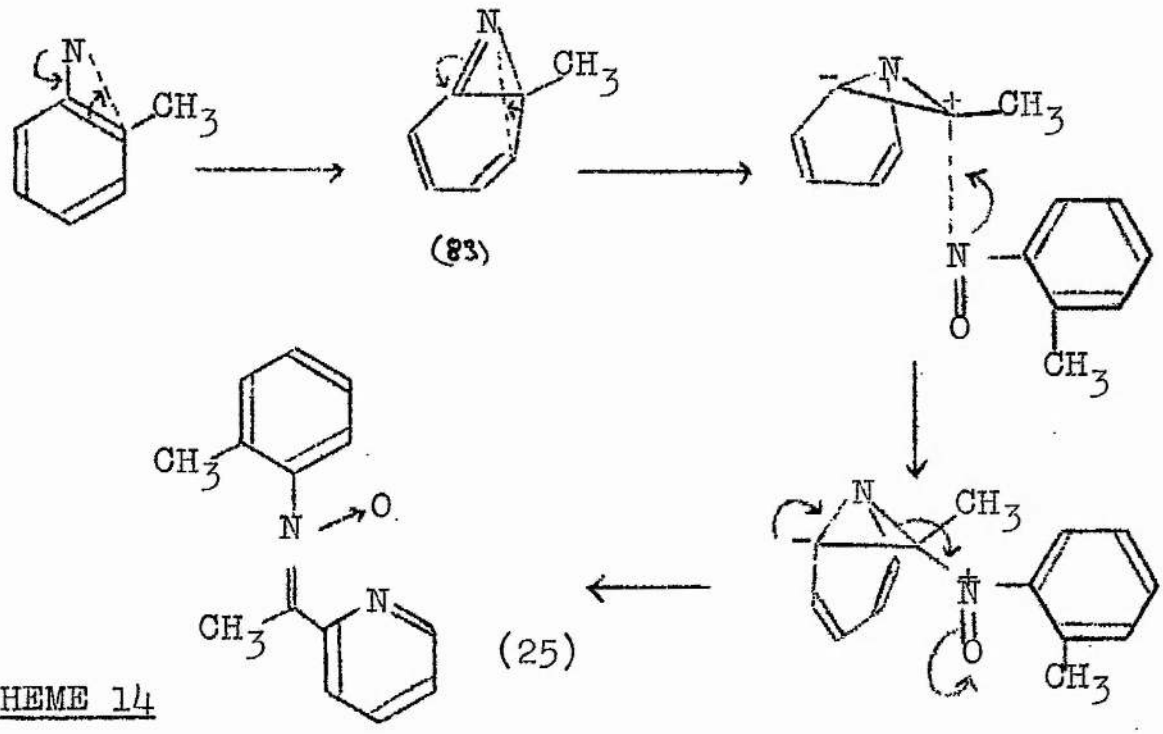
photolytic decompositions of aryl azides. This is presumably due largely to the different rates of formation of the nitrene in each case i.e. whereas photolysis of an azide will generate the nitrene at once in appreciable quantities and in the absence of any other reactant, the deoxygenation of a nitro-group, in particular, takes a considerable time in the presence of a large excess of another reagent with which the nitrene is likely to react very rapidly, once formed. The reaction of trialkyl phosphites with aromatic nitroso-compounds might provide a more convenient rate of reaction: there can be no question, however, of photolytic induction of the reaction, as the photolysis of nitrosobenzene alone is known to give, very readily, a wide range of azoxy- and nitro-benzenes and -anilines.[245]

There are no reports of the isolation of skeletal rearrangement products such as the anil (105) by the photolysis of an aryl azide, in the absence of phosphorus reagents. This may imply merely that, although the

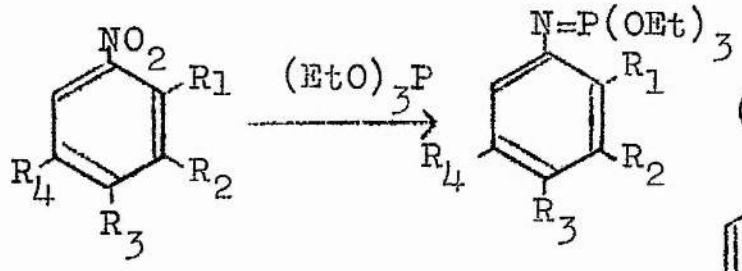


(105)

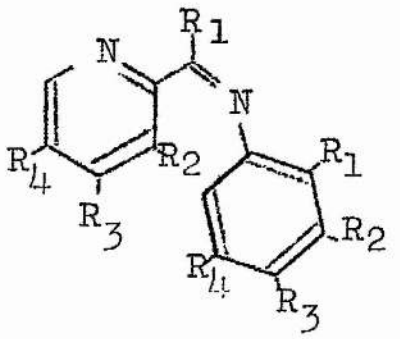
phosphorus reagent is not incorporated into the final product, stabilisation of some reactive intermediate



SCHEME 14



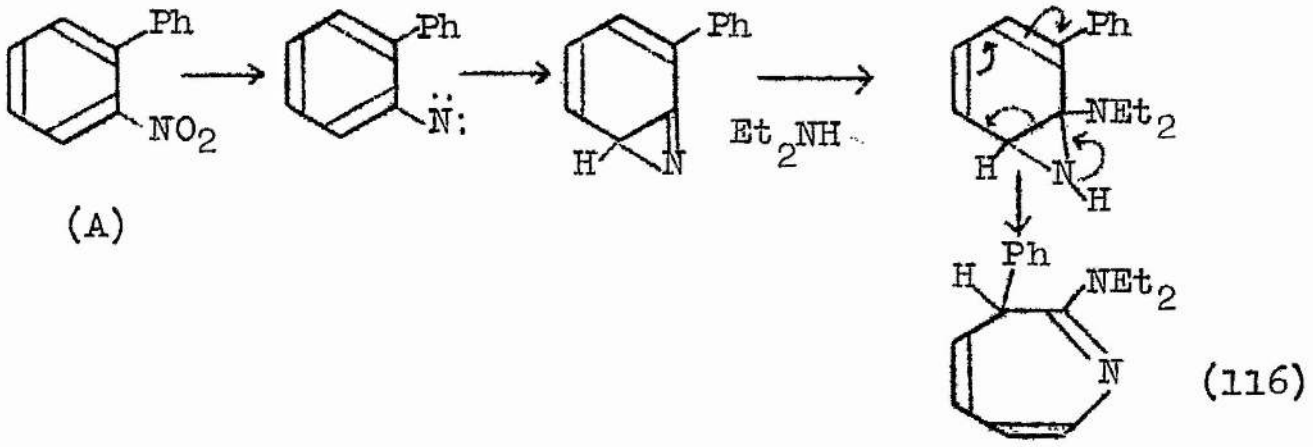
(27) +



(26)

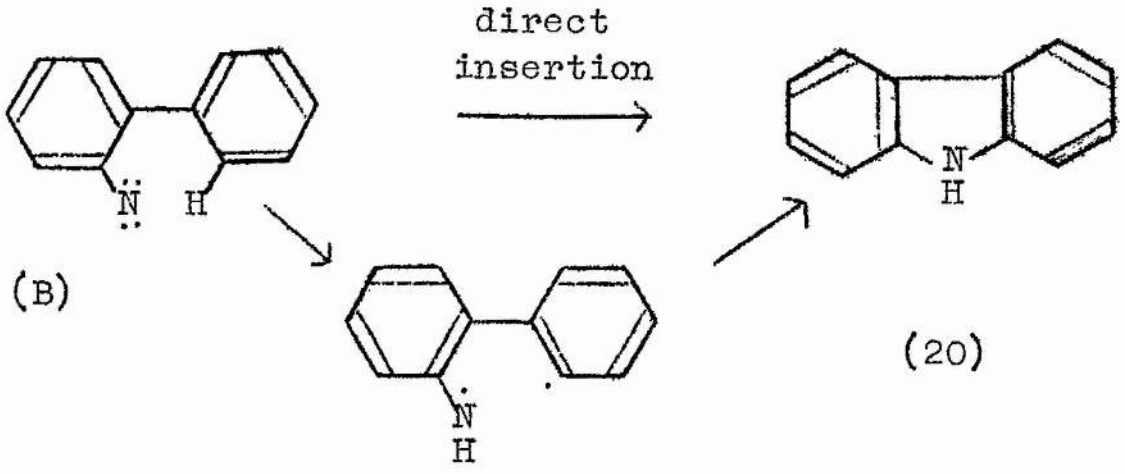
R_1	R_2	R_3	R_4	% (26)	% (27)
H	H	H	H	0	1
H	H	CH_3	H	0	3
CH_3	H	H	H	37	13
CH_3	CH_3	H	H	18	22
CH_3	H	CH_3	H	10	51
CH_3	H	H	CH_3	4	14
H	H	CH_3O	H	0	34

SCHEME 15



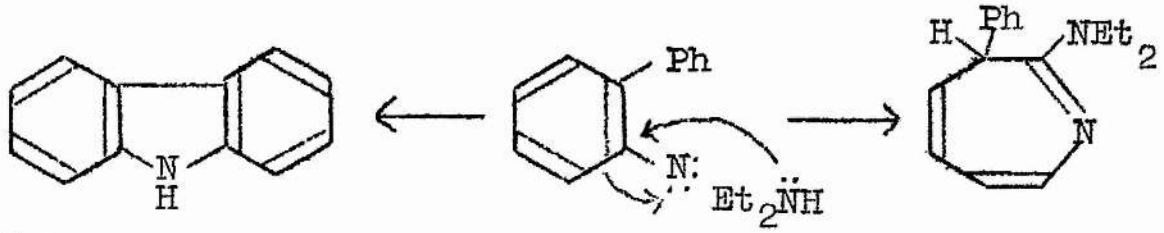
(A)

(116)



(B)

(20)



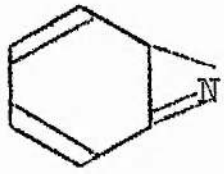
(C)

(116)

SCHEME 30

other than the nitrene is achieved in the presence of trialkyl phosphites: such a mechanism will be discussed shortly.

(iv) The possible rearrangement of the nitrene to other reactive intermediates. The participation in these reactions of the 7-azabicyclo[4,1,0]hepta-2,4,6-triene intermediate (83) has been discussed already (e.g. Schemes 14 and 15).



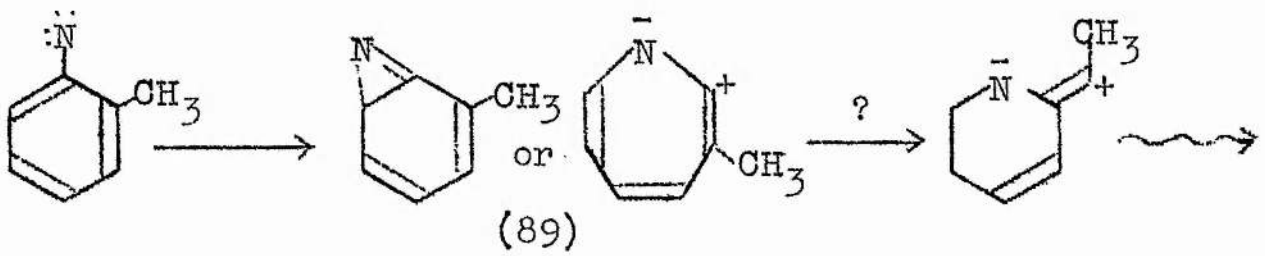
(83)

It is not, however, certain whether this intermediate and the nitrene are successive intermediates, leading eventually to ring expansion and the formation of an azepine, or whether both are present together in equilibrium in the reaction mixture.

The recently reported reaction[147] of diethyl methylphosphonite with 2-nitrobiphenyl, in an excess of diethylamine, to give 2-diethylamino-3H-3-phenyl-azepine (116, 13%) in addition to carbazole (20, 67%), is relevant to this discussion (Scheme 30). While the formation of the azepine (116) may be satisfactorily explained in terms of the mechanism originally suggested by Huisgen et al.[126] (A), the formation of carbazole

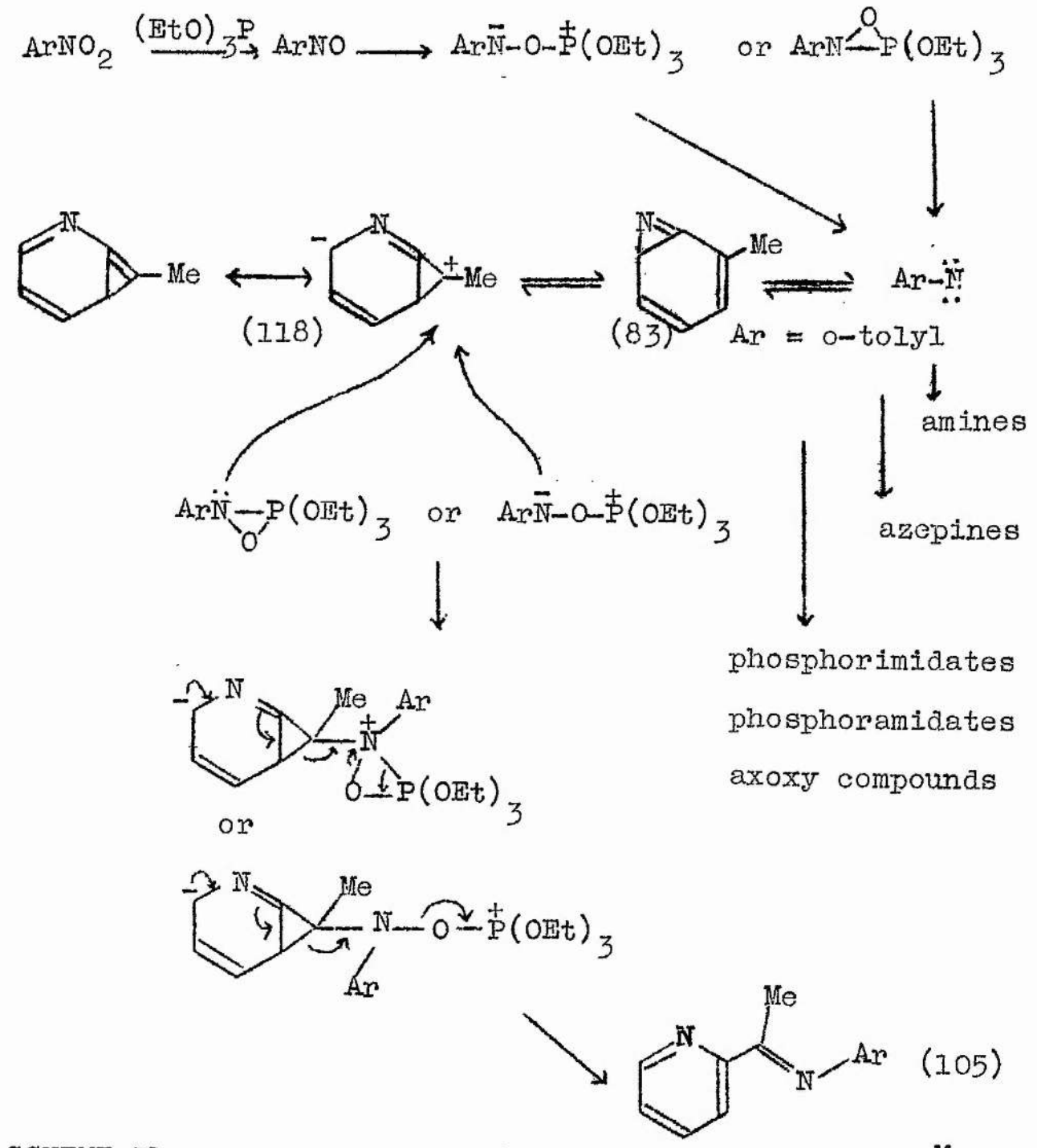
has been taken to indicate attack by the nitrene at the 2'-position of the biaryl, either by hydrogen-abstraction or by direct C-H insertion (B). The possibilities are then that <u>either</u> both azepine and carbazole in fact arise from one intermediate only (presumably the nitrene via (B) and (C), this being a less-strained intermediate than the azabicycloheptatriene system), <u>or</u> that both intermediates are present in equilibrium (as suggested by Abramovitch and Davis[99]) or as a part of a resonance-stabilised system.

The formation of the anil (105) in the thermal[73] and photo-induced[85] reactions of triethyl phosphite with <u>o</u>-alkylnitrosobenzenes does require the participation of intermediates, other than the nitrene, in which the <u>o</u>-alkyl group has some stabilising or directing effect.

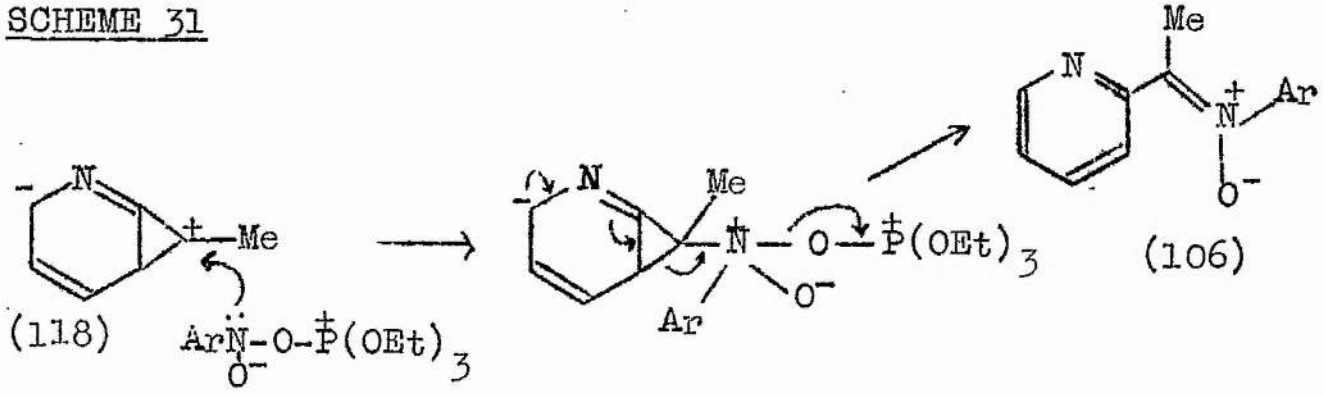


(89)

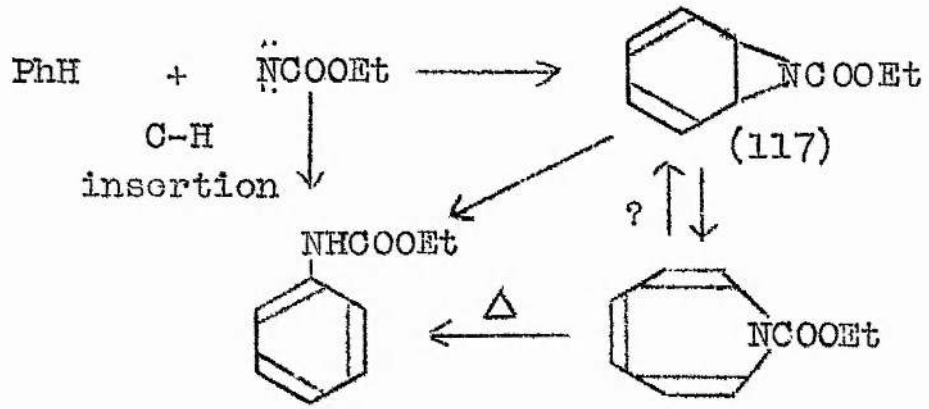
Sundberg was, however, unable to say whether the azabicycloheptatriene or the azepine system (89) was the more likely intermediate.[85]


ArNO2
(EtO)3P
ArNO
ArN̄-O-P̄(OEt)3
or
ArN—P(OEt)3
O
Me
(118)
(83)
Ar = o-tolyl
Ar-N̈
amines
azepines
phosphorimidates
phosphoramidates
axoxy compounds
ArN̈—P(OEt)3
O
or
ArN̄-O-P̄(OEt)3
Me
Ar
O—P(OEt)3
or
N—O—P̄(OEt)3
Ar
(105)

SCHEME 31


Me
(118)
ArN̈-O-P̄(OEt)3
O⁻
N—O—P̄(OEt)3
Ar
O⁻
Me
Ar
O⁻
(106)

The possibility that the azepine system might itself rearrange was discussed earlier (p.26-27), in connection with the formation of the phenylurethan from benzene and N-carbethoxynitrene: while there may be C-H insertion by the nitrene, rearrangement of the azepine through 7-carbethoxy-7-azabicyclo[4,1,0]heptadiene (117) is possible.



It is now suggested, somewhat tentatively in the absence of clear experimental evidence, that a new intermediate (118) may be involved in these reactions (Scheme 31). This does satisfy the skeletal rearrangement requirements determined by Sundberg (Scheme 15).[85] It also requires, however, that the formation of the nitrene ArN from the primary adduct $ArN^{-}\text{-}O\text{-}P^{+}(OEt)_3$ should be considerably slower than the subsequent rearrangement of the nitrene to the other intermediates (83 and 118). While general experience would suggest that the formation of a nitrene from the nitroso-compound is in fact rapid,

there is insufficient kinetic data to distinguish clearly between the various possibilities.

A similar reaction with the "primary adduct" of the nitro-compound and triethyl phosphite with the intermediate (118) would be expected to yield the nitrone (106), reported by Sundberg,[73] although the formation of this compound has not been confirmed in the course of the present investigation.

Whatever the details of the equilibria between the various intermediates, the overall effect remains that there are a number of different possibilities for reaction within this system, with the balance between them being as yet too fine to allow accurate prediction of the product distribution in any particular reaction.

(v) Product formation from the possible intermediates. The formation of the various products from the reaction of tervalent phosphorus reagents with aromatic nitro- and nitroso-compounds may now be considered briefly in the light of the discussion so far.

The formation of the phosphonate (113) has been discussed already, on the assumption that there is no participation by a nitrene intermediate in this reaction.

The formation of azoxy compounds (104) by interaction of a nitrene intermediate with unchanged nitroso-com-

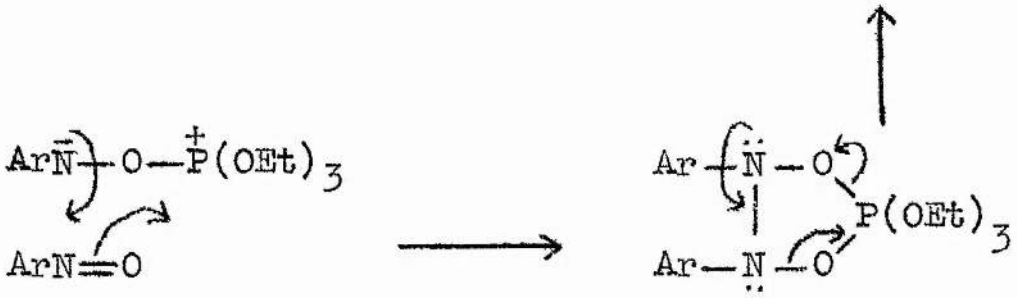
pound has been discussed elsewhere:[72]

$$ArNO + (EtO)_3P \longrightarrow Ar\ddot{\underset{\cdot\cdot}{N}} + (EtO)_3PO$$

$$Ar\ddot{\underset{\cdot\cdot}{N}} + ArNO \longrightarrow ArN{=}N(O)Ar$$

Other routes, not involving a discrete nitrene, are also possible:[17]

$$ArNO\ dimer + (EtO)_3P \longrightarrow ArN{=}N(O)Ar + (EtO)_3PO$$



The formation of the anil (105) and the nitrone (106) is ascribed to the participation of a new intermediate (118), formed from the nitrene, and described in the previous section.

The formation of various amines (107) is typical of the behaviour of nitrene intermediates in other systems, and this would seem to be the most reasonable mechanism in this case. Alkylation of these amines by the trialkyl phosphates present would be expected to take place.[246] Alkylated amines are also produced by the hydrolysis of the dialkyl N-alkyl-N-arylphosphoramidates

in the presence of concentrated acid[190] or by decomposition of the dialkyl N-arylphosphoramidates at high temperatures:[247] neither of these would however seem as likely a means of formation as alkylation by trialkyl phosphates, a known preparative method for such compounds.

If a nitrene intermediate is formed in the course of the deoxygenation reaction, it is difficult, in the light of the well-established preparation of trialkyl N-arylphosphorimidates by decomposition of aryl azides in the presence of trialkyl phosphites,[189] to see why these phosphorimidates (109) should not be formed as major products of the reaction. However, while phosphorimidates are indeed the major products in the controlled deoxygenation of aromatic nitroso-compounds, they appear to be completely absent after the longer and more vigorous reactions with aromatic nitro-compounds. Dialkyl N-alkyl-N-arylphosphoramidates[200] (111) and dialkyl N-arylphosphoramidates[72,73] (110) have been reported as evidence of the prior formation of the trialkyl N-arylphosphorimidates (109). In this present investigation it has been shown that not only is there no evidence for the presence of trialkyl N-arylphosphorimidates in the final reaction mixture, but that the

proportions of phosphoramidate (110) and N-alkyl-phosphoramidate (111) vary considerably with the phosphorus reagent (TABLE 14).

These observations are partially in accord with the results of Gilyarov et al.[190] on the rates of isomerisation of different trialkyl phosphorimidates. It was shown that whereas triethyl N-arylphosphorimidates isomerised relatively slowly, even in the presence of ethyl iodide, to the diethyl N-ethyl-N-arylphosphoramidate the corresponding trimethyl esters isomerised rapidly on heating.

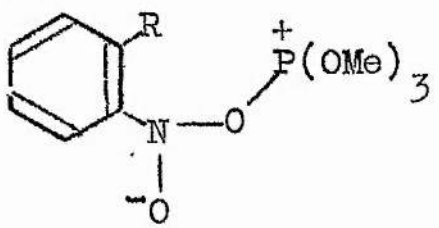
$$(EtO)_3P{=}NAr\cdot R \xrightarrow[\text{slow}]{EtI} (EtO)_2PON(Et)Ar\cdot R$$

$$(MeO)_3P{=}NAr\cdot R \xrightarrow[\text{fast}]{\triangle} (MeO)_2PON(Me)Ar\cdot R$$

It was assumed that the role of methylating agent in this latter case was played by the initial trimethyl N-arylphosphorimidate, since all methyl esters of mineral acids possess methylating powers. The rearrangement of the methyl esters was shown to be temperature dependent - occurring to a considerable extent when they were distilled in vacuo at 150-180°, but to a very small extent only below 100°. In the presence of methyl iodide, the rearrangement was 90% complete

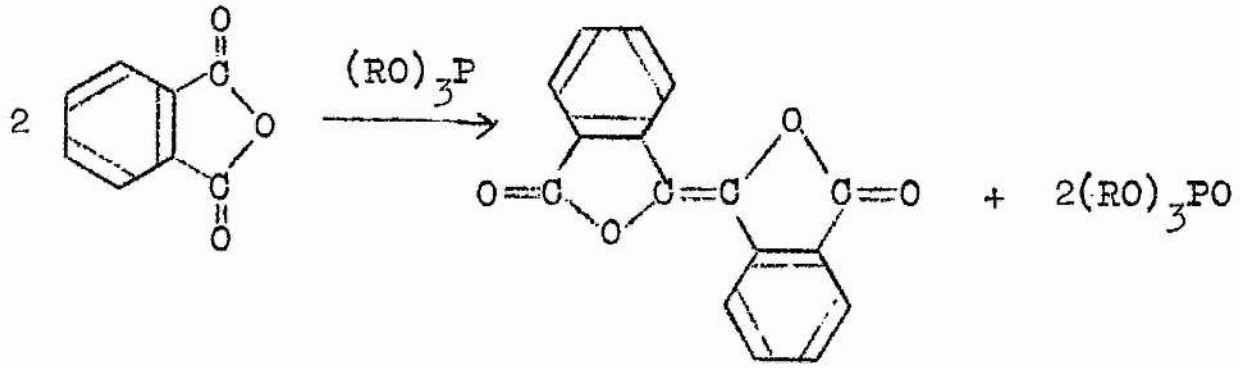
after 24 hours at 18°, whereas the triethyl esters showed no reaction under these conditions.

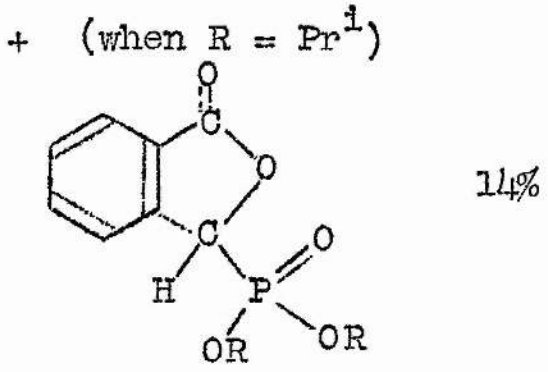
Thus, in the reactions now studied, any trimethyl N-arylphosphorimidate formed would be expected to rearrange at once to the dimethyl N-methyl-N-aryl-phosphoramidate, which would presumably not react further under these conditions. The methylating agent could be the trimethyl phosphate formed in the deoxygenation reaction, or the original trimethyl N-arylphosphor-imidate,[190] or the "primary adduct" acting as a quaternised phosphite ester:[43]

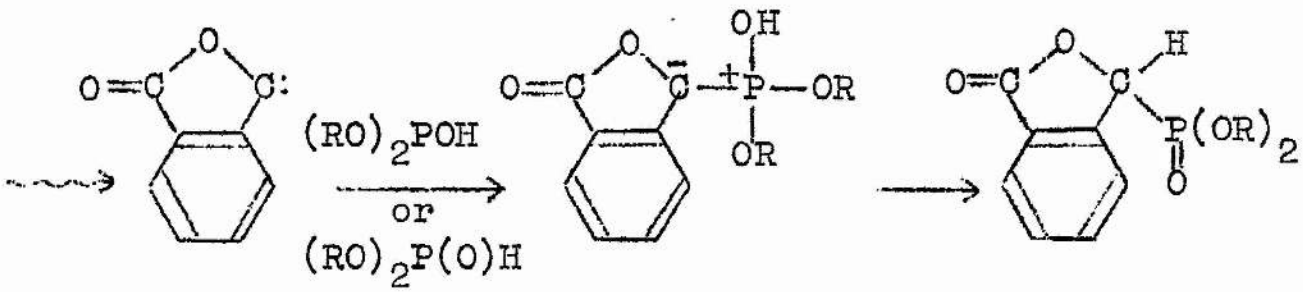


Similar reactions would account for the rearrangement of the excess of trimethyl phosphite to dimethyl methyl-phosphonate. Triethyl N-arylphosphorimidates would not however show this ready isomerisation, and hydrolysis to the corresponding diethyl N-alkylphosphoramidate might become more important, thus increasing the yield of this at the expense of the N-ethyl-N-arylphosphor-amidate.

It has now been shown, however, that dialkyl N-arylphosphoramidates (110) are present in the final

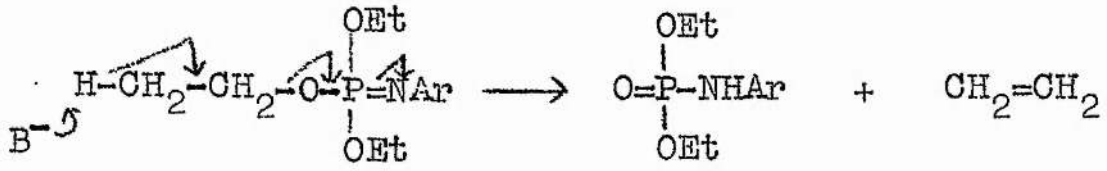




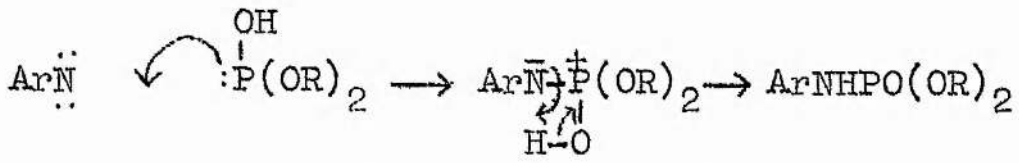


SCHEME 32

reaction mixture and are not formed merely during the extraction of the various products.[72,73] Hydrolysis, by a base, of the trialkyl N-arylphosphorimidates is a possible means of formation of these compounds.

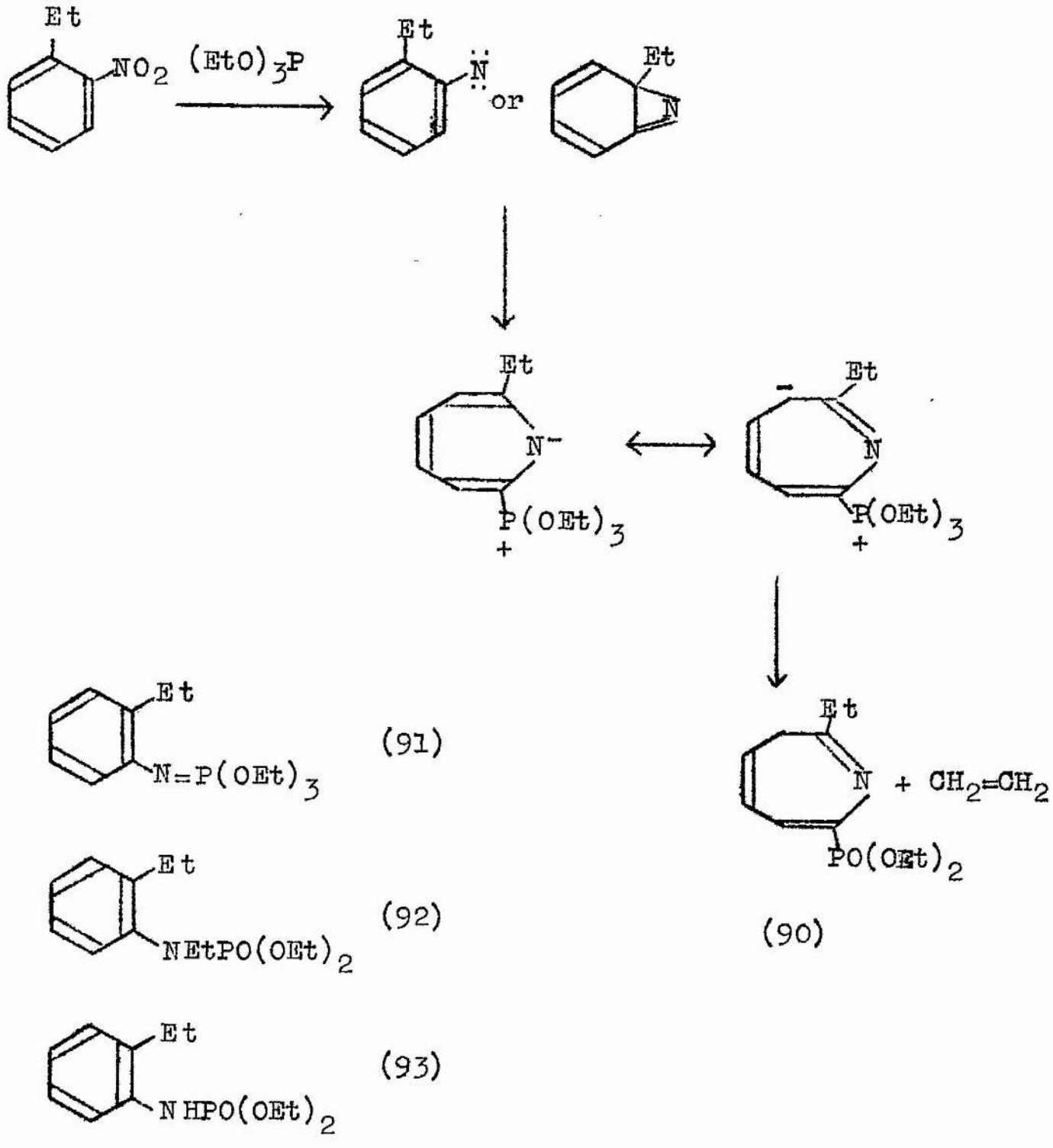


Reaction of the nitrene intermediate with any dialkyl phosphite present would lead to the same product:



Neither mechanism, however, is completely satisfactory as an explanation of the formation of the phosphoramidate as a major product (5-26%) of the reactions.

It is interesting to note that Ramirez[43] reported a similar difficulty in postulating a satisfactory mechanism leading to a side product found in the preparation of biphthalyl from phthalic anhydride (p.8). The reaction of phthalic anhydride with tri-isopropyl phosphite gave di-isopropyl phthalide-3-phosphonate (14%) in addition to the expected biphthalyl (Scheme 32). The formation of this phosphonate requires a source of hydrogen atoms: as neither propylene nor acetone could


Et
NO2
(EtO)3P
Et
N
or
Et
N
Et
N-
P(OEt)3
+
Et
N
P(OEt)3
+
Et
N
+ CH2=CH2
PO(OEt)2
(90)
Et
N=P(OEt)3
(91)
Et
NEtPO(OEt)2
(92)
Et
NHPO(OEt)2
(93)

SCHEME 18

be detected, it was suggested that the formation of the phosphonate was due to the presence, in the reaction mixture, of small amounts of either water, or of the dialkyl phosphite. Thus, if a carbene was formed in the course of the reaction, the phthalide phosphonate would in turn be formed by direct insertion of the carbene in the H-P bond of $H\text{-}PO(OR)_2$, or by electrophilic attack on the phosphorus atom of the tautomer $P(OH)(OR)_2$, as shown.

In a different series of experiments, however, Todd[200] was unable to detect the presence of any diethyl phosphite in commercially available triethyl phosphite, following the normal method of purification (p.46). Thus the mechanism leading to the formation of the di-isopropyl phthalide-3-phosphonate, as described above, or of the dialkyl N-arylphosphoramidates, described prior to that, must remain uncertain.

Finally the formation of the azepine (112) must be considered. A mechanism for this has been proposed (Scheme 18).[146] Additional support for this mechanism was provided by the isolation of ethylene as a low-boiling product of the reaction. However, two further points must be considered, following this present

investigation.

Firstly, when a liquid-air cold-trap is used in an attempt to condense ethylene and ethyl nitrite as products of the reaction of triethyl phosphite with p-nitrotoluene and p-ethylnitrobenzene, ethylene is indeed found, but in considerably greater quantities (20 and 25 m. mole) than can be accounted for by the formation of the azepine (ca. 5 and ca. 3 m. mole). Even allowing for the difficulty of estimation of the two quantities, a considerable discrepancy does exist. Three possibilities exist:- (i) that the two quantities are, in fact unrelated, the formation of ethylene being in no way dependent upon azepine formation; (ii) that ethylene is formed during the rearrangement to the azepine and also in some other reaction, such as the base hydrolysis of the trialkyl N-arylphosphorimidates, described above; and (iii) that ethylene is formed only during the rearrangement to the azepine and the discrepancy is due to subsequent breakdown or further reaction of the azepine system. Further experimental evidence relating to all deoxygenation reactions is necessary before these possibilities may be distinguished, although the last possibility is perhaps the most reasonable, the elimination of ethylene being a

relatively unusual reaction. Reports of the elimination of various olefins by the thermal decomposition of various dialkyl alkylphosphonates[42,248] are not thought to be relevant at this point, extreme conditions of temperature being generally necessary for such decompositions.[248]

Secondly, while the mechanism is adequate for the formation of diethyl 2-alkyl-3H-azepin-7-ylphosphonates, the isolation of the same azepine ring system from the reaction with trimethyl phosphite, with, of course, differing ester groups, requires either a different mechanism for the formation of the methyl ester of the azepine or an alternative, common, mechanism for both reactions. The formation of considerable quantities of dimethyl methylphosphonate in these reactions suggests that the final dealkylation of the phosphonium intermediate may be taking place in this way: however, as this isomerisation would be expected anyway, this cannot be taken as clear evidence for such a process.

ABSTRACT

The reactions of tervalent phosphorus reagents with a number of aromatic nitro-compounds have been investigated. While it was expected that such reactions would give further examples of the deoxygenation and further reaction of the nitro-group, possibly via a reactive nitrene intermediate, in fact, two, different, novel displacements of the nitro-group were found.

In the first case, reaction of o-dinitrobenzene and related compounds with tervalent phosphorus reagents gave a series of phosphonates, phosphinates and phosphine oxides, in high yield, with the phosphorus atom bonded directly to the aromatic system, generally with an o-nitro-group still present in the final product. A mechanism involving nucleophilic aromatic substitution by the phosphorus reagent, with the displacement of the nitro-group as ethyl nitrite, was suggested.

In the second case, reaction of p-nitrotoluene and p-ethylnitrobenzene, for example, with triethyl phosphite, gave low yields of diethyl p-tolyl- and p-ethylphenylphosphonate. As there is no activation of this nitro-group towards aromatic nucleophilic substitution, a mechanism involving attack on an oxygen of the nitro-group by the phosphorus reagent, with subsequent rearrangement through a four-membered intermediate

was proposed.

The other products of the reactions of o-alkylnitrosobenzenes and alkylnitrobenzenes with trialkyl phosphites were, in general, indicative of the participation, in the reaction, of a nitrene intermediate. The similarity of the products formed to those found in established examples of the reactions of nitrene intermediates, was noticed. The mechanism of this reaction was discussed in detail.

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